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OVULATION INDUCTION DRUG THERAPY FOR ANOVULATORY INFERTILITY ASSOCIATED WITH POLYCYSTIC OVARY SYNDROME

Paula Corabian, Ann Scott

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Ovulation induction drug therapy for anovulatory infertility associated with polycystic ovary syndrome

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This Health Technology Assessment Report has been prepared on the basis of available information of which the Foundation is aware from public literature and expert opinion, and attempts to be current to the date of publication. It has been externally reviewed. Additional information and comments related to the report are welcome and should be sent to:

Director, Health Technology Assessment
Alberta Heritage Foundation for Medical Research
Suite 1500, 10104 - 103 Avenue NW
Edmonton, Alberta T5J 4A7
CANADA

Tel: 780-423-5727, Fax: 780-429-3509

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ABBREVIATIONS/GLOSSARY

Abbreviations

ACOG: American College of Obstetricians and Gynecologists

ADA: American Diabetes Association

AE: adverse events

ART: Assisted Reproductive/Reproduction Techniques

BBT: basal body temperature

BMI: body mass index

BP: blood pressure

CC: clomiphene citrate

CC: resistant/resistance – resistant/resistance to CC therapy

CCTR: Cochrane Controlled Clinical Trials Register

CI: confidence interval

COH: controlled ovarian hyperstimulation

CT: computed tomography

DTRP6: decapeptyl CR: 3.75mg microcapsules

ESHRE: European Society for Human Reproduction and Embryology

$E_{(2)}$ or E_2: serum estradiol

FDA: Food and Drug Administration

FSH: follicle-stimulating hormones

GH: growth hormone

GnRH: gonadotrophin releasing hormone

GnRHa: GnRH analogue (agonist or antagonist preparations)

HbA1c: glycosylated hemoglobin

HCG or hCG: human chorionic gonadotrophin

HDL: high-density lipoprotein

HMG or hMG: human menopausal gonadotrophin

HTA: Health Technology Assessment

i.m.: intramuscular(ly)

IUI: intra-uterine insemination

IU: international unit

IV: intravenous

IVF: in vitro fertilization

IVF-ET: in vitro fertilization and embryo transfer

LH: luteinizing hormone

LOD: laparoscopic ovarian diathermy

LPD: luteal phase defect

mo: month(s)

MPA: medroxyprogesterone acetate

MRI: magnetic resonance imaging

NHS: National Health Service

NSS: not statistically significant

OC: oral contraceptive

OHSS: ovarian hyperstimulation syndrome

OI: ovulation induction

OR: odds ratio

OSS: ovarian stimulation syndrome

P_4: mid-luteal serum progesterone

PCO: polycycstic ovary

PCOS: polycystic ovary syndrome

pFSH: pure urinary FSH

PRL: serum prolactin

RCT: randomized controlled trial

RevMan: Review Manager

rFSH: recombinant FSH

rhCG: recombinant human chorionic gonadotrophin

rhFSH: recombinant human FSH

rGH: recombinant growth hormone

s.c.: subcutaneous(ly)

SHBG: sex hormone binding globulin

SS: statistically significant

T: testosterone

uFSH: urinary FSH

uhCG: urinary human chorionic gonadotrophin

US: ultrasound or ultrasonography

USA: United States of America

vs.: versus

y: year(s)

WHO: World Health Organization

Wk: week(s)

17-∝-OHP: 17-∝-hydroxyprogesterone (a fasting serum)

Glossary [1]:

Amenorrhea: absence or abnormal stoppage of the menses;

Anovulation: absence of ovulation

Infertility: diminished or absent capacity to produce offspring; the term does not denote complete inability to produce offspring as does sterility; called also relative sterility

Oligo-menorrhea: infrequent menstrual flow occurring at intervals of 35 days to 6 months

Oligo-ovulation: ovulation occurring less frequently than normal (Cumming, personal communication)

Parity: the condition of a women with respect with her having borne viable offspring

Primary infertility: infertility occurring in patients who have never conceived

Secondary infertility: infertility occurring in patients who have previously conceived

Sub-fertile: the state of being less than normally fertile; also called relative sterility

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SUMMARY

- Ovulation induction using drugs (OI drug therapy) is the most performed therapy in reproductive-aged women with anovulatory infertility.
- Anovulatory infertility is associated with polycystic ovary syndrome (PCOS) in the majority of cases and it appears to be difficult to manage safely and successfully with OI drug therapy in this population.
- The reviewed evidence was obtained from randomized controlled studies of small to moderate sample size, short duration, and limited methodology. The investigators used different approaches, treatment protocols, study population, definitions of outcome measures and types of outcomes.
- The question on which is the safest and the most effective OI drug therapy in these women does not have a clear answer yet. According to the available evidence:
    - ➢ CC therapy remains the first choice of OI drug therapy because of its relative safety, effectiveness in achieving ovulation, simple mode of administration and relatively low cost. However, success in achieving ovulation equates with success in achieving pregnancy in only half of cases. The increased risk of multiple pregnancies associated with the use of CC should also be considered.
    - ➢ In women who do not ovulate or do not conceive in response to CC therapy, gonadotrophin therapy is the next medication of choice. It is still not certain whether any type of gonadotrophin preparations currently available is superior in terms of improving pregnancy rates and reducing complication rates. Low-dose gonadotrophin regimens (regardless of preparations used) may be considered in order to reduce the incidence of multiple follicle developments and the associated complications.
    - ➢ Metformin as a pre-treatment and co-treatment with CC seems successful in increasing chances of achieving pregnancy in selected cases and has been proposed as a sequential treatment before the use of gonadotrophins. However, data regarding its use alone or as an adjunct to CC remain to be confirmed before recommending it as a standard therapy.
    - ➢ The clinical utility of using pulsatile gonadotrophin releasing hormone (GnRH) therapy for this indication remains to be established.
    - ➢ There is no clinical advantage in the routine use of GnRH analogue in addition to gonadotrophin therapy for this indication.

  - ➢ The role of using other adjuncts in addition to CC therapy or to gonadotrophin therapy for this indication has yet to be firmly established.

- OI drug therapy using gonadotrophins should be restricted to centers with the expertise and the equipment necessary to make appropriate clinical decision relating to the treatment and management of the associated complications.

- Women with PCOS considering OI drug therapy to manage their anovulatory infertility should be aware that :

  - ➢ regardless of the approach used, they appear to be at increased risk for multifollicular development and spontaneous abortion;

  - ➢ the risk of developing serious complications such as multiple pregnancies and ovarian hyperstimulation syndrome appears to be higher when gonadotrophin therapy is used; and

  - ➢ there may be a reduced probability of a male live birth following CC therapy.

Large scale RCTs, well-designed and conducted, on the use of various approaches to OI drug therapy for longer time are needed to provide definitive evidence on their value in managing anovulatory infertility associated with PCOS. An accurate and detailed sub-classification of women with PCOS may have important implications in the search for the safest and most effective OI drug therapy for this indication.

Data on the overall cost of using various approaches to OI drug therapy are needed to aid in the couple's decision-making and to assist in the formulation of policy for using this therapy to manage this indication.

INTRODUCTION

This report is a systematic review and critical appraisal of the evidence on the use of ovulation induction (OI) drug therapy to manage anovulatory infertility associated with polycystic ovary syndrome (PCOS) in women of reproductive age. The aim was to provide the current published scientific evidence about its safety and efficacy/ effectiveness in terms of pregnancy rate in this category of infertile patients in response to a request for information from Alberta Health and Wellness.

The inability to conceive because of ovulation dysfunction leads many women to use OI therapy to manage their anovulatory infertility. In women of reproductive age, PCOS is estimated to be the most common cause of anovulatory infertility [2, 3, 4, 5, 6, 7, 14].

Approaches to OI therapy for anovulatory infertility associated with PCOS may include OI drug therapy (alone or combined with other drug therapies and/or interventions) or surgical procedures [7, 8, 9, 10, 11, 12, 13, 14]. Among all OI treatments, drug therapy remains the most common and is primarily indicated for reproductive-aged women with anovulatory infertility [15, 9, 11, 16]. It has been regarded as an established intervention for this indication.

However, OI drug therapy for management of anovulatory infertility associated with PCOS continues to evolve as new knowledge on how to manage this condition for different subgroups of patients emerges [2, 3, 4, 5, 6]. Because of the opportunities in the clinical and basic science of OI, new therapies have been developed and used in the last 10 years. Currently, many approaches to OI drug therapy are in widespread use for this indication. However, none of these therapies has become unique in achieving pregnancy safely in all cases.

SCOPE OF THE REPORT

Approaches to safe and effective OI drug therapy to manage infertility have been the subject of many evaluations and discussions. OI drug therapy using different agents has been used within two main distinct contexts [3, 15, 16, 17, 18, 19]: as a medical therapy for anovulatory infertility and also as an adjunct for assisted reproductive technologies (ARTs), such as intra-uterine insemination (IUI), *in vitro* fertilization (IVF) and variations of IVF. OI drug therapy has been used (in both contexts) alone or in combination with other therapies for a variety of indications, such as infertility associated with ovulation factors or disorders, infertility due to endometriosis, male infertility and unexplained infertility.

This report is not intended as a comprehensive review of all OI agents used (alone or in combination with other therapies) for the management of infertility in all contexts. Rather, this assessment is focused on reviewing and critically appraising the published literature on the use of OI drug therapy alone for management of anovulatory infertility associated with PCOS in women of reproductive age because of the interest regarding this topic in Alberta. The intent was to respond to the question on "which OI drug therapy could be a safe and effective procedure to be used in women of reproductive age who suffer from PCOS and anovulatory infertility and want to achieve pregnancy".

This review **does not cover**:

- the use of OI drug therapy (alone or in combination with other therapies) as a preparatory step to promote maturation and multiple egg development in ovulatory women undergoing ARTs;
- the use of OI drug therapy (alone or in combination with other therapies) for other causes of infertility (alone or co-existing);
- the use of OI drug therapy combined with other therapies to treat anovulatory infertility associated with PCOS or the use of other types of OI therapy (such as surgical induction of ovulation) to treat this cause of infertility in women resistant to OI drug therapy.

The final report of the Royal Commission on New Reproductive Technologies, issued in 1993, was used as background material for this assessment. The Canadian Government established the Commission in 1989 to study the impact of assisted reproduction on the Canadian society. It also reviewed the evidence on the effectiveness, side effects and risks of using fertility drugs for anovulatory infertility. The focus of the present review has been on the primary and secondary research studies published since the completion of the Royal Commission's report (see Appendix A, B, and C for more details on the methodology used).

The report consists of four main sections. The first section is a narrative review of overview articles, commentaries and discussions providing background information that defines the clinical problem and describes the OI drug therapy.

The second section is a narrative review of the published information on various OI drug therapy approaches used to manage anovulatory infertility associated with PCOS. A summary of the recommendations from guidelines and position papers issued since 1993 on the use of OI drug therapy for this indication are provided. This section also summarizes the information published after 1993 on the regulatory status, coverage and costs for OI drug therapies. Information about various OI drugs' mechanism of action, clinical indication, method of administration, risks and complications associated with their use, and contra-indications is presented in Appendix D.

The third section presents information published on the use of OI drug therapy and its cost and coverage in Canada. This section also summarizes the Royal Commission's findings regarding the OI drug therapies used in Canada for infertility caused by ovulation dysfunction during late 1980s and early 1990s.

The fourth section presents the available scientific evidence published since 1993 on the use of OI drug therapy alone for the management of anovulatory infertility associated with PCOS. It summarizes the findings of this review of the literature, which has provided more recent evidence on the safety and efficacy/effectiveness of the OI agents described in the second section. The efficacy/effectiveness of OI drug therapy is considered in terms of pregnancy rates. A discussion of the findings from this review, their implications for clinical practice and the conclusions are also presented in this section.

The main features, reported results of interest and main conclusions of the primary and secondary research studies included in this review are summarized in a tabulated form in Appendix E.

SECTION I: BACKGROUND

CLINICAL PROBLEM

Infertility (also termed as relative sterility or subfertility) is a condition characterized by a reduction in the ability to reproduce or achieve conception [9, 20]. One of the most common causes of infertility in women of reproductive age is ovulation dysfunction (20%-40%) which disrupts (or even shuts down) the normal reproductive cycle [7 10, 9, 13, 15, 19, 21, 22, 23, 24,] (http://www.asmr.org).

Ovulation is the result of a well-synchronized balance between hormones produced by the brain, hypothalamus, pituitary gland and ovary [6, 25]. The follicle-stimulating hormone (FSH) and the luteinizing hormone (LH) are two hormones (known as gonadotrophins) produced to stimulate the ovaries to produce other hormones and to prepare female reproductive cells (eggs or ova) for maturation and release. Both these hormones are responsible for ovarian follicular growth, likely acting by the intermediacy of specific growth factors. When a single, dominant egg is ready for release, a large, one-time release of LH, known as the LH surge, signals the ovary to release the one mature egg.

Any disruption of the complex interactions of the hormones from the hypothalalmus-pituitary-ovary axis can lead to ovulation dysfunction and impair the reproduction process [2, 6, 7, 26]. Ovulation dysfunction is a term that describes a group of disorders in which ovulation fails to occur, or occurs on an infrequent or irregular basis. Failure to ovulate is generally indicated by the absence of menstruation (amenorrhea) or infrequent menstruation (oligomenorrhea). Without ovulation, fertilization and pregnancy do not occur. This type of infertility is referred to as anovulatory infertility.

Anovulatory infertility

Anovulatory infertility is defined as a condition in which there is no or infrequent rupture of follicles of the ovaries with the subsequent release of an ovum (the female reproductive cell)[9]. Although ovulation dysfunction can be caused by many factors, most of the ovulation disorders are related to female hormonal imbalances [2, 6, 7, 26].

There is a spectrum of conditions between total anovulation and normal ovulation [2, 6, 7, 9, 10, 15, 22, 23, 26]. Anovulatory infertility has been mainly associated with four conditions found with relatively high frequency in women with suspected ovulation dysfunction attending infertility clinics [27].

These conditions include [2, 6, 9, 15, 19, 24, 27, 28, 29]:

1. hypogonadotrophic anovulation, classified by the World Health Organization (WHO) as pertaining to infertility group 1 (WHO group 1);

2. normogonadotrophic anovulation, classified by WHO as pertaining to infertility group 2 (WHO group 2);
3. hypergonadotrophic anovulation; and
4. hyperprolactinemic anovulation.

Anovulatory infertility associated with conditions classified as WHO group 1 and WHO group 2 has been estimated to represent almost 30% of all causes of infertility [19]. In clinical practice WHO group 2 subjects present much more frequently than WHO group 1 subjects and they appear to be much harder to treat successfully [2, 7, 9, 15, 22, 30, 31]. Among women classified as WHO group 2, those diagnosed with PCOS constitute the largest group (60-85% of cases) [2, 3]. These women account for most cases with oligo-menorrhea (90%) and represent about 30% of those with amenorrhea [6, 7, 8, 13, 14, 15, 32, 33, 34].

Polycystic ovary syndrome (PCOS)

PCOS is a complex, heterogeneous endocrine disorder. It includes a spectrum of conditions rather than a single discrete disease [2, 6, 8, 18, 24, 25, 31, 34, 35, 36, 37, 38, 39, 32, 40, 41, 42, 43, 44]. Someone with PCOS may have one or all of the following symptoms in varying degrees: the appearance of typical polycystic ovaries on ultrasound, irregular or absent menses and ovulation, infertility, characteristic of hyperandrogenism (such as hirsutism and acne), and obesity.

The exact criteria necessary for an accurate and differential diagnosis of the syndrome remain an area of considerable debate. A confounding factor is the lack of consensus regarding the definition of the syndrome [6, 12, 32, 35, 36, 37, 39, 45]. Some investigators suggested a combination of clinical, ultrasound and biochemical criteria to diagnose PCOS [7, 8, 11, 25, 34, 35, 37, 39, 46, 47, 45].

The primary cause and pathophysiology of PCOS and the main factors that preclude menstrual cyclicity in women suffering from this syndrome have not been fully elucidated [6, 12, 25, 32, 36, 34, 35, 37, 39, 40, 41, 45, 47, 48]. To date, insulin resistance, androgen excess, abnormal gonadotrophin secretion and genetic predisposition have been suggested as important factors. Recently, it has been suggested that the insulin resistance (which occurs in both lean and overweight or obese women with PCOS but is most evident in overweight or obese women) and the consequent hyperinsulinaemia play a key role and contribute to hyperandrogenism and anovulation [5, 12, 25, 27, 32, 34, 36, 35, 37, 40, 42, 44, 46, 47, 49, 50, 51].

Some evidence suggests that obesity (body mass index or BMI > 28-30 kg/m^2) [5], a prominent and common feature in PCOS, is also an important pathogenetic factor. It is thought to be involved in the development of hyperinsulinaemia and to have a gonadotrophic function that contributes to hyperandrogenism and anovulation [6, 24, 25, 27, 30, 31, 32, 34, 35, 40, 44, 45, 46, 52]. Hypersecretion of LH, another common endocrine abnormality in PCOS, is also believed to interfere with folliculogenesis, resulting in anovulation and poor quality oocytes [5, 9, 14, 34, 38, 39, 53, 54].

MANAGEMENT OF AVOVULATORY INFERTILITY ASSOCIATED WITH PCOS

Because the primary cause of PCOS is still unknown, management of anovulatory infertility associated with this syndrome is based on the overall clinical picture, which includes variables such as age, duration of infertility, degree of the ovarian and adrenal androgen excess, and presence of weight and insulin resistance problems. Meticulous evaluation and examination to establish a differential diagnosis of PCOS before initiating the treatment is very important [6, 9, 18, 27, 28, 32, 49, 55, 56, 47]. This approach is recommended to rule out other disorders potentially problematic for the woman's general health and for optimizing her chances of achieving successful pregnancy by using the appropriate intervention.

Lifestyle modification has been suggested as the first line of therapy to induce ovulation in these women before considering medical therapy in order to improve the chance of a successful outcome [6, 8, 9, 14, 24, 27, 30, 32, 34, 37, 40, 42, 44, 49, 50, 51, 52, 53, 57]. In those who are overweight or obese, some evidence suggests that, together with exercise, weight loss may reduce androgen levels and hyperinsulinemia, and improve ovulatory function and pregnancy rates[14, 49, 53]. However, some women need alternative approaches as they seem incapable of initiating and/or maintaining weight loss by lifestyle modification [44].

For women who fail to lose weight, normal weight women who suffer from hyperinsulinemia and its consequences, and when weight loss fails to restore ovulation, management of anovulatory infertility associated with PCOS by using OI drug therapy is the next suggested step [6, 8, 9, 24, 27, 32, 37, 42, 44, 49 50, 51, 52, 53].

OI drug therapy

OI therapy is an infertility treatment that allows women to ovulate and have the chance of conceiving naturally. The principle of this therapy is to stimulate the ovaries to produce a single mature (dominant) follicle, to induce ovulation, and to allow fertilization and pregnancy to occur by natural intercourse [2, 3, 6, 7, 8, 10, 11, 15, 17, 18, 19, 22, 26, 49, 50].

OI therapy using pharmacological agents (refered to here as OI drug therapy) is the predominant intervention used for anovulatory infertility in women categorized into WHO group 1 and WHO group 2 (including those with PCOS) [2, 6, 7, 8, 10, 11, 15, 17, 18, 22, 26, 49, 50]. Although the cause of anovulation will guide the selection of an appropriate treatment plan for these women [24, 44] the main steps of this therapy include:

- proper and comprehensive diagnostic evaluation and clinical examination of the potential candidate to establish a correct and differential diagnosis, and exclude other disorders and possible causes of anovulation and infertility;
- correcting any underlying factors, if present, and optimizing health before commencing OI drug therapy;
- provision of appropriate medication to stimulate one single egg or ovum to mature;
- close and careful monitoring of the treatment cycles (by ultrasonography and/or biochemical tests) to examine the ovary response, individualize drug doses and prevent side effects and complications;
- administration of ovulation triggers (timed by ultrasonography with respect to the size and number of developing follicles), where appropriate, to cause the final maturation and release of one egg;
- sexual intercourse, timed to coincide with the treatment-induced ovulation; and
- pregnancy testing.

Other approaches to OI therapy include surgical induction of ovulation procedures [8, 10, 11, 12, 15, 18, 24, 58]. However, the use of surgical procedures to induce ovulation in these women is beyond the scope of this review.

Factors influencing response to OI drug therapy

In women with anovulatory infertility associated with PCOS, one of the main goals of OI drug therapy is to avoid multiple follicular developments that may result in over-stimulation, leading to cycle cancellation and complications such as multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). Polycystic ovaries (PCOs) appear to be highly sensitive to the OI agents currently available and have a tendency toward multiple follicular recruitment [2, 9, 12, 18, 37, 39, 41, 59, 60, 61, 45].

A variety of OI drugs have been used in these women, but none of them are unique in terms of safety and efficacy in achieving pregnancy. The development of so many approaches is related to the syndrome's multifactorial pathophysiology, the variability in the clinical manifestations and to the abnormal hormonal background [2, 3, 4, 9, 12, 15, 24, 32, 34, 37, 38, 39, 45, 46, 52, 53, 62, 63].

The syndrome's heterogeneity is reflected in the different responses to the various OI drugs [2, 3, 4, 5, 9, 12, 15, 18, 30, 32, 34, 37, 38, 39, 45, 46, 52, 53, 54, 55, 59, 60, 61, 62]:

- the elevated LH levels (present in ~40% of women with PCOS) may adversely affect the outcome of treatment by reducing the conception rate and increasing the spontaneous abortion/miscarriage rate [5, 9, 34, 38, 39, 53, 54];
- the hyper-androgenic state may also adversely affect the response to treatment [9, 15];

- obesity and insulin resistance may result in hyper-androgenism and cause poor response [9, 12, 30, 37, 39, 45, 52, 53]; OI drugs appear to be less effective when BMI>28-30 kg/m^2 [5]; insulin resistance and the compensatory hyper-insulinemia may increase the risk for OHSS [45]; and
- the polycystic ovaries may be resistant to drugs even after the administration of relatively high doses of medication [39].

SECTION II: OI DRUG THERAPY APPROACHES

OI DRUG THERAPY APPROACHES

The following commentary presents information on the use of OI drug therapy to manage anovulatory infertility in reproductive-aged women with PCOS. The most frequently used medical approaches for this indication include clomiphene citrate (CC), and gonadotrophin therapy (with or without adjuvants) for those women who do not respond to CC (do not ovulate or do not conceive). More recently, agents acting as insulin sensitizers have been proposed and used in these women.

A summary of the information (published since 1993 in overview articles, commentaries and discussions) regarding these therapies' mechanism of action, administration mode, clinical indications and contraindications, risks and complications and their side effects is provided in Appendix D.

1. CC therapy

CC is a non-steroidal estrogen receptor antagonist agent, most commonly used as the first line treatment for OI in women with levels of estrogen in the normal range and normal levels of FSH and prolactin including those with PCOS (for more information on CC, see Appendix D). Tamoxifen, another anti-estrogen agent, has also been used for this purpose, in a manner similar to CC but less frequently [49, 64].

Anovulatory infertility in reproductive-aged women with PCOS appears to be difficult to manage with CC therapy. The final activity of CC may be influenced by many factors such as woman's age, metabolism, dosage regimen, administration period relative to the cycle, cause of anovulation, and estrogenic state, as well as carry-over effects from previous CC cycle(s), and effects of unknown metabolites [39, 65, 66]. Although there currently are no data to reliably predict response to CC in these women [52], it appears that the efficacy of CC therapy is decreased in the presence of obesity, hyperandrogenemia, elevated testosterone concentrations and severe insulin resistance [24, 66].

The CC therapy induces ovulation in 60% to 85% of cases but only about half of these women become pregnant [8, 11, 15, 22, 25, 26, 30, 31, 34, 39, 48, 49, 52, 53, 55, 59, 67, 68, 69, 70]. The reason for resistance to CC (CC-resistance) is poorly understood [12, 21, 26, 39, 49, 52, 53, 55]. Women who do not ovulate after CC tend to be overweight [21, 25, 34, 39, 52, 66, 71] and the main reason for their anovulation seems to be the lack of follicle maturation even though their pituitary shows an appropriate response to increasing FSH secretion [39]. Low growth hormone levels were also proposed as one of the mechanisms for CC resistance in these women [72].

The lower pregnancy rate in relation to ovulation rate has been attributed to the anti-estrogenic effects of CC and its metabolites on the cervical mucus, the endometrium and possibly the oocytes [5,15,21,22,39,49,55,65,72,73]. It has been suggested that in some women with "markedly elevated androgen and insulin levels" the endometrial proliferation may not be compromised by CC use but by their "abnormal hormonal milieu" [74]. Another possible reason is the increase in basal LH secretion induced by CC, which may also account for early pregnancy loss in some patients [5,21,39,75].

Alternative and adjunct therapies

Given the lack of ovulatory response to CC in a small but significant minority of PCOS cases, and the problem of ovulatory cycles without conception, prolonged duration of CC or higher doses of CC have been tried in an attempt to enhance the chances for success [21,31,39,53]. Some evidence positively correlated the ovarian response to and the dose of CC with body weight [3,50,52,66,71], and OI attempts with increasing dosages have been considered justified in overweight patients [50,52,53]. Extending the duration of CC therapy has also been tried in some patients [31,39,53,55].

Combinations of CC with other drugs such as glucocorticoids, bromocriptine, and tamoxifen have been used, more frequently in the past, in previously unresponsive patients [11,15,18,24,25,31,39,49,50,55,76]. Another adjunct used in CC cycles was human chorionic gonadotrophin (hCG), an ovulation trigger [9,24,31,39,49,50,55,58].

More recently, some evidence suggested that anovulatory women with PCOS who do not respond to CC therapy (fail to ovulate or conceive despite ovulation) show greater insulin resistance than women with PCOS who ovulated successfully in response to CC [21,66]. Metformin, an insulin sensitizing agent, has been used as an adjuvant to enhance CC response in these women [24,32,34,44,50].

The most frequently advocated OI alternatives for patients who are not responsive to CC therapy include gonadotrophin therapy and surgical treatment [5,8,11,12,15,18,25,30,31,32,39,40,48,49,52,53,58,67,70,77]. Although there are no generally accepted criteria to indicate which method should be selected according to the individual patient's clinical and laboratory features, gonadotrophin therapy has most commonly been suggested as the next appropriate option [8,9,15,18,25,30,31,32,39,40,48,49,52,53,67,77].

2. Gonadotrophin therapy

Gonadotrophin therapy has been widely used in women who were unresponsive to CC therapy (failed to ovulate or become pregnant despite ovulation after CC). Some investigators suggested that this therapy is indicated for CC-resistant women with infertility associated with PCOS if they have persistent hyper secretion of LH and negative post-coital tests due to the anti-estrogenic effect on the cervical mucus [5,18] (see Appendix D for more information on gonadotrophin therapy and various injectable gonadotrophin preparations).

It has been suggested that when using gonadotrophin therapy for anovulatory infertility associated with PCOS, achieving the formation of a single dominant follicle and avoiding multiple follicular development and its associated complications depend on the type and dose of the preparation administered [3, 18, 30, 55, 60, 61, 69, 78]. The use of pure FSH preparations (containing only FSH) has been proposed as an alternative to human menopausal gonadotrophin (HMG) preparations (containing both FSH and LH in various ratios) with the aim of increasing pregnancy rates and reducing complication rates in these women [3, 5, 11, 18, 31, 32, 48, 49, 53, 68, 69, 78, 79, 80, 81].

However, the administered dose appears to be much more important than the preparations used. Because the polycystic ovary is very sensitive to stimulation with these hormones, it has been recommended to start with low doses of gonadotrophins [15, 18, 23, 24, 28, 32, 39, 48, 49, 53, 55, 56, 61, 82]. Low dose therapy, with pure FSH preparations or with HMG preparations has been suggested as more efficient than standard/conventional dose therapy in preventing multiple follicular developments and the associated complications [3, 5, 11, 18, 31, 32, 48, 49, 53, 79, 68, 69, 78, 80, 81].

Low-dose gonadotrophin therapy does not appear to improve pregnancy rates [3, 5, 18, 31, 32, 48, 49, 53, 69, 78, 79, 81]. It has been suggested that the most significant factors adversely influencing pregnancy rate are age, excess in body weight and insulin resistance [5, 48]. It appears that higher dosages are required to achieve ovulation in insulin resistant women. Obese women being treated with low-dose therapy may have lower pregnancy rates. Miscarriage rates tend to remain the same (~ 30%) for women with PCOS, regardless of the use of a low-dose regimen [31, 53].

Alternative and adjunct therapies

Beyond the use of various low-dose regimens of gonadotrophin therapy, other strategies have been developed with the aim to improve the reproductive outcome in these women in terms of achieving successful pregnancy and reducing the risk for OHSS, multiple gestation, and miscarriages. These include the use of pulsatile gonadotrophin releasing hormone (GnRH) therapy and the use of pre-stimulation protocols using combined oral contraceptive pills and/or a GnRH analog therapy. More information on these therapies is provided in Appendix E.

Some evidence suggested that the use of pulsatile GnRH therapy may reduce the incidence of OHSS and multiple gestations [15, 55]. However, it does not appear to increase pregnancy rates and the reported abortion rates are high [15, 39, 41, 53, 55].

Pre-treatment with GnRH analog (GnRHa) therapy does not seem to prevent OHSS and/or improve pregnancy rates [19, 23, 25, 31, 39, 41, 53, 54, 59, 69, 83, 84, 85, 86, 87] but it may decrease the high spontaneous abortion rate in these women [31].

Some other drugs have been used as adjuncts to gonadotrophin therapy with the aim to improve the outcome in terms of achieving successful pregnancy and reduce the risk for complications in this population [3, 24, 25, 49, 88, 89]. These include dexamethasone for adrenal androgen suppression, dopamine agonists (when hyperprolactinemia is also present), growth hormone (GH) (hypothesized to improve ovarian responsiveness) and metformin (as an insulin-sensitizing agent).

3. Insulin-sensitizing agents

Given the belief that hyperinsulinaemia has an important role in PCOS, insulin sensitizers have been advocated to address the ovulatory dysfunction related to insulin resistance and hyperandrogenism [5, 25, 32, 34, 42, 43, 49]. Among the agents currently available on the market, only metformin and rosiglitazone have been evaluated as therapies for anovulation associated with PCOS. For more information on metformin and rosiglitazone, see Appendix D.

Metformin is the agent studied in most detail and in the largest group of anovulatory women with PCOS. It is believed to have a role by itself or in combination with CC or with gonadotrophin preparations in inducing ovulation and achieving pregnancy in appropriately selected women who are resistant to CC therapy [12, 21, 24, 25, 32, 33, 34, 37, 49, 50, 90, 91, 92, 93]. It has been suggested that metformin should be used in women with clinical evidence of insulin resistance who have failed to achieve pregnancy following weight loss and CC therapy [34].

Among other characteristics found for women who have previously been shown to favour response to metformin, Sturrock et al. [90] cited a higher BMI, higher fasting insulin and lipid concentrations, higher blood pressure, lower androstenedione concentrations, and less severe menstrual irregularities.

It has been suggested that lean women with PCOS who are not insulin resistant or hyperinsulinemic may not tolerate all insulin sensitizing agents [37].

Intensive monitoring is not required during metformin treatments and available evidence indicate a negligible risk of OHSS and multiple pregnancy when this drug is used alone [93].

Rosiglitazone has been recently suggested as an alternative to metformin for this indication in obese or overweight women [94]. This consideration was based on the side effect profiles of the two agents. After 3 years of clinical use, rosiglitazone has not been associated with the gastrointestinal side effects commonly reported with metformin (which may limit patient compliance).

GUIDELINES AND POSITION PAPERS

Recommendations from guidelines and position papers issued on the use of OI drug therapy suggest that [9, 18, 24, 28, 55, 56, 61, 95]:

1. Careful and meticulous diagnostic investigations are necessary before any OI drug therapy is considered. The investigations should include laboratory assessment of ovulation, evaluation of tubal patency and semen analysis.
2. Potentially reversible causes of anovulatory infertility should be addressed and women's health should be optimized before OI drug therapy is started. In overweight or obese women with PCOS, weight loss should be considered before commencing drug therapy.
3. Use of OI agents should be restricted to appropriately investigated couples with a diagnosis in whom the proposed treatment has been shown to be beneficial in view of its safety and efficacy.
4. CC therapy is the treatment of choice for anovulation in appropriately selected women (including those with inappropriate gonadotrophin release, or increased LH to FSH ratio, as occurs in PCOS) and only up to 12 cycles should be considered.
5. Treatment with gonadotrophins (both HMG and FSH) is an effective OI therapy in women with low levels of estrogen and gonadotrophin and is also useful in women with PCOS who failed to respond to CC therapy. It should be given in low dose regimens in specialized clinics that permit access to daily, careful and intensive monitoring of ovarian response.
6. The pulsatile administration of GnRH is effective only in selected women, those with anovulation due to hypothalamic factors or hypothalamic amenorrhea.
7. There is no advantage in routinely using GnRHa in conjunction with gonadotrophins in women with CC-resistant PCOS (no increase in pregnancy rate and potential increased risk of developing OHSS).
8. Women with polycyctic ovaries may be more sensitive to treatment regimens used for ovulatory dysfunction and require particular vigilance for use of GnRHa and gonadotrophins.
9. Centres should use only OI drug therapy protocols that minimise the risk of multiple pregnancy and OHSS.

Given the present lack of long-term safety data and demonstrable efficacy of metformin in achieving successful pregnancy and live births in a large number of patients with anovulatory infertility associated with PCOS [24, 42, 43, 47], it has been recommended that its use (to address ovulation dysfunction associated with insulin resistance) be supervised by an endocrinologist or physician with expertise in the area [42].

The guidelines and position statements emphasized the importance of counseling patients/couples before the therapy starts [9, 18, 28, 42, 43, 47, 55, 56, 61]. Prior to treatment, candidates must be given information about the process of OI drug therapy to ensure realistic expectations. The risks and complications associated with the agent under consideration for the mother and fetus, as well as chances of success, would need to be outlined.

REGULATORY STATUS AND COVERAGE

CC therapy is approved by the Food and Drug administration (FDA) in the United States of America (USA) for use in anovulatory amenorrhea and oligomenorrhea [25]. According to Aetna U.S. Healthcare®, most plans cover the use of oral CC (Clomid®, Serophene®) for OI in female infertility cases [96].

Injectable agents may be covered when used for OI in case of failure to conceive after treatment with "Basic Infertility Services" [96, 97, 98]. Some plans may limit coverage of OI to 6 cycles with menotropins per lifetime. Aetna covers only injectable agents intended to be self administered when an appropriate oral alternative drug does not exist [98]. Many plans exclude coverage for injectable agents used for infertility [96].

The following agents may be covered when used to induce ovulation for female infertility [96, 97]:

- GnRH such as Gonadorelin (Lutrepulse®, Factrel®), and Leuprolide (Lupron®):
  - Leuprolide (Lupron®) is covered when used in conjunction with urofollitropin or menotropins to suppress LH production in patients with documented premature LH surge [97]. It is not covered for PCOS and hypermenorrhea since only limited information has been published on its use for these conditions and further research is required to determine its efficacy for these indications.
- hCG such as A.P.L.®, Pregnyl®, Profasi®, Chorex®, Choron®;
- HMG (menotropins) such as Pergonal®, Humegon®, Repronex®;
- recombinant FSH (rFSH) such as Follitropin alfa (Gonal-F®) and Follitropin beta (Follistim®)); and
- Urofollitropin (human FSH) such as Fertinex®.

Metformin and rosiglitazone are currently approved by FDA for use in the management of type 2 diabetes but not for OI drug therapy [24, 34, 66] (http://www.fda.gov/cder/onsumerinfo/druginfo/avandia.htm).

COSTS

There are many costs related to infertility management, those covered by the health care plans and drug insurance plans as well as those paid by the patients/couples receiving the treatment. These costs include direct costs associated with diagnosis, treatment and treatment monitoring. They also include medical costs due to complications of treatment and costs to the patient or the health care system incurred during pregnancy, delivery or the neonatal period. Costs associated with infertility management also include indirect costs (incurred by the patient) such as costs for transportation to the provider and for accommodation or time off from work.

Costs for OI drug therapy

The success of OI drug treatment in terms of pregnancy rate achieved depends on many factors, particularly on the disease severity (type, cause and duration of infertility), and women's age [17,18,22,48,55,58]. The therapy can be as simple as taking a daily pill or more complicated, like injecting medications and daily specialist visits for necessary monitoring. Some drug treatments involve careful timing, self-injections, and potentially serious complications.

Costs for OI drug therapies vary among various centers, as they depend on the type and dose of medication required, number of cycles, duration of therapy, injection training (if necessary), the number of visits and the number of ultrasound and blood tests (if any) required for an adequate monitoring throughout each cycle. Also prices for these drugs vary.

Depending on how much medication is required and what type of and how much therapy monitoring is performed, a CC cycle may cost between $50 and $700 (USD) (http://www.babycenter.com) [17]. One cycle of CC has been reported to cost $330, which included drugs, blood tests, ultrasound and the necessary physician visits [58]. This estimate (which considered prices in the USA in the early 1990) did not include time lost from work or expenses of travel to and from the clinic.

The cost of using gonadotrophin therapy is much higher. Injectable gonadotrophins cost between $35 and $70 (USD) per ampoule [17,23]. This therapy requires frequent specialist visits for appropriate monitoring and guidance (which can include bloodwork, ultrasounds, or just verbal counseling in regards to dosing and injection techniques as injections are often self-administered or administered by the partner) [18,28,55,23]. Monitoring of each cycle is essential when using gonadotrophin therapy, which adds substantially to the cost of a cycle.

The cost of a cycle using HMG ranges between $1,000 and $4,000 (USD), depending on which preparation is used, how much medication the patient requires and how much and what type of monitoring is performed [17, 23, 58]. An estimate (based on prices in the USA in the early 1990s) suggested that one cycle of HMG cost about $1,400 (median costs) [58]. This estimate included drugs, blood tests, ultrasound, and the necessary physician visits. However, it did not include time lost from work or expenses of travel to the clinic. Using rFSH preparations appears to be much more costly [19].

According to recent Medicaid data [90], the cost for meformin is low (ranges between $25 USD for Glucophage XR® 500 mg and $49 USD for Glucophage® 500mg), lower than the cost of rosiglitazone (($174 USD for Avandia® 4mg).

A cost analysis of an OI drug therapy should include costs of complications and consequences of treatment, such as costs associated with care for OHSS, ectopic pregnancy, miscarriage or premature delivery due to multiple pregnancies. Also, estimates should include indirect costs such as those associated with time lost from work or expenses of travel to the clinic.

SECTION III:
OI DRUG THERAPY IN CANADA

OI DRUG THERAPY IN CANADA

Estimates suggest that infertility affects 330,000 Canadian couples [74, 100]. Eighty-four percent of these couples suffer from diminished fertility (or subfertility), while in 10% of these couples the woman is sterile (bilateral tubal obstruction) and in 6% of cases the man is sterile (absence of sperm) [74]. This represents 8.5% of all couples in which the female partner was aged 15-44 years and who have been married or co-habiting for at least one year [20, 70, 100]. It has been estimated that 45% of these infertile couples sought medical assistance to achieve pregnancy in 1995 [100].

Pharmacological interventions constitute the majority of infertility treatments in Canada and CC and HMG are the most commonly used for infertility associated with ovulatory defects [15, 16, 100]. Collins et al. [100] projected the distribution of infertility treatments in Canada in 1995 using data on treatments used by 2198 couples seen in Canadian infertility clinics from 1984 to 1991. According to their projections, 12% of the infertile couples sought medical care and chose CC (10%) or HMG (2%) as their initial treatment for ovulation defect.

Unpublished results from a survey of 1500 Canadian family physicians (cited by Collins et al. [100]) found that CC was prescribed on a regular basis by 11% and occasionally by 34% but other types of infertility treatments were rarely used. A companion survey of 500 Canadian obstetricians/gynaecologists (also cited by Collins et al. [100]) found that 88% prescribed CC for infertile patients and 15-20% offered more complex treatments such as HMG.

ROYAL COMMISSION'S FINDINGS [16]

The effectiveness and safety of these drugs when used for anovulatory infertility were of interest to the Royal Commision on New Reproductive Technologies [16] who reported their findings in 1993.

The two criteria used by the Commission to conclude whether or not an OI drug therapy could be categorized as "a treatment that is of benefit" were as follows:

1. the drug had to have been tested and been shown of benefit in appropriately designed randomized controlled trials with at least 200 subjects in each of the control and treatment groups; and
2. the drug has to be shown clearly to affect a specific pathway or factor known to cause infertility there had to be a clear and plausible biological reason for the drug to work.

If the reviewed evidence did not show that the OI drug therapy met one of these two criteria, the Commission judged it unproven (that is "the evidence is insufficient to say whether use of the drug is either better or worse than receiving no treatment").

The Commission found that the biological mechanism of action of CC for ovulation disorders was feasible. The CC therapy was generaly accepted to be an effective treatment for all ovulation disorders and became a standard treatment for them. The published literature (consisting of few randomized controlled trials of small sample size and several other studies) reported pregnancy in 30% to 40% of women treated with CC. However, it cautioned that the practitioners often overestimated the success rates obtained with CC.

The Commission concluded that CC has been proven effective and of low risk "when used at the approved doses" to treat lack of ovulation resulting from diagnosed primary and secondary amenorrhea, and oligomenorrhea and it should be considered as an "accepted treatment" for this indication. Because of the lack of data from large-scale studies, the Commission recommended that women considering the use of CC for anovulation "should be informed about the limited availability of reliable data on its use" and that "the effects of the dosages used should be monitored closely".

For gonadotrophin therapy, the Commission found that there is "a clear and plausible biological mechanism by which hMG works" and it has been observed that the drug is effective in producing ovulation in many women with amenorrhea or oligo-menorrhea who did not respond to CC. Although, it has more risks and complications associated with its use than CC therapy, the Commission concluded that HMG could be an appropriate treatment for anovulatory women (with amenorrhea) who have not responded to CC therapy.

However, there was insufficient evidence to conclude whether treatment with HMG was effective for women with oligomenorrhea and irregular cycles who did not respond to CC. Women with oligomenorrhea still ovulate, and in theory they still have a chance to become pregnant without treatment. There was "no convincing evidence that hMG corrects a specific biological pathway in this situation" and the Commission concluded that HMG was "of unproven value" for this indication.

In the Commission's assessment, the use of GnRH was found to be effective for the treatment of women with amenorrhea caused by Kallman syndrome and should be considered medically necessary for this indication. The therapy worked through a precise and convincing biological mechanism.

The Commission also searched for evidence published since 1955 about adverse effects of OI drugs and the evidence revealed that:

- The most serious side effect was OHSS, which depending on the drug used could be mild, moderate, or severe. Severe cases were rare but can be life threatening.
- There was an increased rate of multiple pregnancy and births. The use of HMG carried the greatest risk, with multiple pregnancy rates reported as many as 32%.
- There was a need for further research to estimate whether there was an increased risk of developing ovarian cancer following use of OI agents and if so to determine its magnitude.
- The incidence of congenital anomalies among children of women who underwent OI drug therapy was found to be similar to that in the general population.
- Further research was needed to determine long-term health effects on women and their children.

A meta analysis from the Royal Commission on New Reproductive Technologies [101] indicated that the use of CC may be associated with a significant reduction in the live birth sex ratio (usually reported to be about 105 liveborn males per 100 liveborn females) [102]. The reported meta-analysis data showed a reduction in the sex ratio from 1.051 to 0.96 (males:females) [101].

Since the the reported reduction noted in Canada and the United States from 1970 to 1990 [102] there is increasing interest in the evaluation of the sex ratio. Recently, this effect has been analyzed in terms of single and multiple births and noticed among patients from a variety of countries, including Canada [103]. The identified lower probability of a live born male following CC therapy suggests potential interactions of CC on the embryo development. The mechanism is unknown, but may be due to the estrogenic and anti-estrogenic properties of CC therapy through actions on the estrogen receptors of the female.

REGULATORY STATUS AND COVERAGE

A search of the Drug Product Database of Health Canada revealed the following agents [104]:

- Clomiphene citrate (Clomid® and Serophene®, 50mg tablets, manufactured by AVENTIS PHARMA INC., PHARMASCIENCE INC., and SERONO CANADA INC.), classified as an estrogenic agonist-antagonist agent;
- HMG preparations (Humegon® and Pergonal®, injection 75 IU, manufactured by ORGANON CANADA LTD. and SERONO CANADA INC.), classified as gonadotrophins;
- rFSH (follitropin alpha) preparations (Gonal-F®, manufactured by SERONO CANADA INC), classified as gonadotrophins;
- rFSH (follitropin beta) preparations (Puregon® -50 IU, 100IU, 300IU and 600 IU, manufactured by ORGANON CANADA LTD.), classified as gonadotrophins;
- hCG preparations (Pregnyl®, Profasi HP® and Profasi HP 10000®, injection 10000 unit/vial, manufactured by ORGANON CANADA LTD., PHARMASCIENCE INC., and by SERONO CANADA INC.), classified as gonadotrophins; and
- GnRH agonist (nafarelin) preparations (Synarel®, manufactured by PFIZER CANADA INC.), as an unclassified therapeutic agent;
- GnRH preparations such as:
    - Gonadorelin (Lutrepulse PWS®, 0.8 mg/vial,, manufactured by FERRING INC.) as gonadotrophins;
    - Gonadorelin (Relisorm 100®, and Relisorm 500®, injection – PWS Liq-Kit IV sc - manufactured by SERONO CANADA INC.) classified as pituitary function agent;

Metformin hydrochloride (various products, manufactured by various companies) and rosiglitazone (Avandia®; manufactured by GLAXOSMITHKLINE INC.) are available in Canada and are approved for use as miscelaneous antidiabetic agents [104].

The Society of Obstetricians and Gynaecologists of Canada (SOGC) recommended that patients entering treatment for infertility be advised regarding the limitations of their insurance coverage since the use of OI agents is associated with a considerable potential cost [105].

In Canada fertility drugs and/or treatment coverage varies across provincial government formularies [106]. According to Serono-Canada, CC is covered for the first line of infertility treatment only in Quebec and there is no government formulary coverage in the other provinces and territories [106].

COSTS

Information on the overall direct costs of managing infertility in Canada is scant. According to the most recent estimates, 26% of the infertile couples seeking medical advice or treatment in 1995 had live births associated with these services costing CDN $415 million [100]. The majority of these costs arose from causes of infertility that were most difficult to treat.

Collins et al. [100] estimated the cost of CC therapy for ovulation defect (*the type of ovulation defect was not specified*) in 1995 at CDN $229. This estimate was based on the average prescription charge in Central West Ontario ($35 per cycle for six cycles plus $19 for the follow-up visit) and did not include the costs for monitoring the CC cycle.

The 1995 cost of CC therapy per live birth for ovulation defect was estimated at CDN $674 [100]. This estimate was calculated by dividing the annual cost of treatment per patient (CDN $229) by the proportion of cycles that resulted in a live birth. The calculation considered an expected probability of a live birth after 6 CC cycles of 34%. Diagnostic costs were not included.

Collins et al. [100] also estimated the 1995 cost of HMG therapy for ovulation defect (*the type of ovulation defect was not specified*) at CDN $1,600 per treatment cycle. This estimate included costs associated with clinic visits, procedures, monitoring and medications.

The 1995 cost of HMG therapy per live birth for ovulation defect was estimated at CDN $11,163 [100]. This estimate was calculated by dividing the annual cost of CDN $4,800 per treatment per patient ($1,600 for 3 cycles) by the proportion of cycles that resulted in a live birth. The calculation considered an expected probability of live birth after 3 HMG cycles of 43%. Diagnostic costs were not included.

The live birth rates for these therapies were derived primarily from trial results [100]. Collins et al. [100] cautioned that although they were "the most accurate estimates available", they were crude estimates of the average cost per live birth. These figures do not provide information comparing the incremental cost of one clinically relevant treatment plan relative to the cost of a clinically relevant alternative plan for the same indication. Neither do they take into account any systematic differences among categories of the "quality" of the live births, such as the incidence of multiple pregnancies and prematurity.

The study did not include costs for the care of complications associated with that treatment (such as OHSS, ectopic pregnancy, miscarriage and premature delivery due to multiple pregnancy), since data were not available for all treatments.

SECTION IV:
PUBLISHED SCIENTIFIC EVIDENCE

EFFICACY/EFFECTIVENESS AND SAFETY

The decision of using a given OI agent in the treatment of anovulatory infertility associated with PCOS is based on its effectiveness, side effects, the severity of the associated complications, costs and coverage, and the patient's/couple's personal choices. Among all these components, the safety and efficacy/effectiveness of a given agent are critical issues.

The efficacy/effectiveness can only be judged fairly based on results obtained from randomized controlled trials (RCTs) since conception can occur in many infertile couples over time without treatment, even when the infertility condition is of a long duration [9, 15, 16, 20, 23, 58].

The intended goal of using OI agents to manage anovulatory infertility in women with PCOS is to correct ovulatory dysfunctions and enable a couple to achieve pregnancy and live birth of a healthy child. For this review the effectiveness of OI drug therapy was evaluated by selecting primary and secondary research studies, which reported reproductive outcome data in terms of pregnancy rates. Although live birth rates and take-home baby rates are preferable, the majority of published studies reported pregnancy rate as the most relevant measure of reproductive outcome.

Also considered in this assessment were the risks and complications most frequently associated with the use of OI drug therapy such as miscarriages, multiple pregnancies, and OHSS.

Primary research studies

The literature search yielded 44 primary research studies on the use of various OI drug therapies in anovulatory infertility (including both WHO groups 1 and 2). Only twelve of the identified studies [54, 68, 75, 86, 88, 94, 107, 108, 109, 110, 111, 112] met the inclusion criteria as described in the methodology section (see Appendix A). The remaining 32 studies were excluded and reasons used for their exclusion are provided in Table 2, in Appendix C.

The main features, reported results of interest, and main conclusions of the all 12 inlcuded studies (all RCTs) are summarized in Table 3, in Appendix E. An assessment of these studies' methodological quality is provided in Table 4, Appendix E.

Description of the reviewed RCTs

All RCTs, except the RCT by Parsanezhad et al. [109], recruited fewer than 100 women Participants in all RCTs were infertile/subfertile women with PCOS. PCOS was diagnosed and defined in most trials as a combination of clinical features, and/or abnormal endocrine tests and/or ultrasonographic or visual appearance of the ovaries, which differed from trial to trial (see Table 3, Appendix E). The syndrome was defined as a combination of clinical features, ovarian appearance on ultrasound, and endocrinological abnormalities in five trials [54, 68, 86, 110, 111] a combination of the first two criteria in three trials [88, 109, 112]; a combination of the first and last criteria in two trials [94, 107]; and not defined in two trials [75, 108]. Some of these studies describe in detail the criteria used to diagnose PCOS while others just list them.

In most trials, the patients had previous CC treatment and were resistant to it (or failed to respond) [54, 68, 83, 86, 88, 94, 109, 110, 111]. Most investigators included women who only failed to ovulate after CC therapy [68, 86, 88, 94, 109, 111]. One study included women who failed to conceive after CC therapy [54]. One other study included women who failed to ovulate or to conceive after CC therapy [110]. In each of these categories, different definitions of CC-resistance were used in terms of maximum dosage, days, and duration of administration. Details on the maximum administered dose and/or number of days and cycles were not provided in one trial [54].

Lidor et al. [75] included women who had previous CC treatment, but no information was provided on whether or not they failed to respond to the treatment in terms of ovulation or pregnancy. In the report of the RCT by **Ramzy et al.** [112] no information is provided on whether enrolled women were CC-resistant or not.

The information on baseline characteristics considered as important prognostic factors for OI drug therapy success such as age, type of anovulatory infertility, parity, duration of infertility, BMI, and presence/absence of other causes of infertility was not provided in all 12 RCTs. Information on age was provided in ten RCTs [49, 54, 68, 75, 86, 88, 94, 109, 110, 111.] (mean values varied from 24.9 years to 32.4 years).

Information on BMI was provided in nine trials [54, 68, 86, 88, 94, 109, 110, 111, 112]. These trials included women with various BMIs (mean values varied from 22.3kg/m^2 to 38.4 kg/m^2). Information on infertility duration was provided in eight RCTs [54, 68, 75, 86, 88, 107, 109, 110] with mean values ranging from 2.5 years to 5.2 years. Information on parity was provided only in three RCTs [75, 94, 107] and information on tubal patency was provided in eight RCTs [54, 86, 88, 109, 110, 111, 112]. Information on partner's semen analysis was provided in ten studies [86, 88, 107, 108, 109, 110, 111, 112].

Each RCT evaluated different OI drug therapies and different approaches to and protocols for these therapies. One RCT compared the use of CC with pulsatile GnRH [107]. Another RCT [108] studied the effect of pre-treatment with kenocotazole on CC responsiveness. The RCT by **Parsanezhad et al.** [109] evaluated the effects of administering bromocriptine combined with CC.

Six studies evaluated various gonadotrophin preparations when used alone in various protocols or when used in combination with various adjuvant therapies. One of these studies [110] compared 2 low-dose FSH regimens. Four studies looked at the effects of using GnRHa as an adjunct therapy to urinary gonadotrophin preparations [54, 68, 75, 86].

One study evaluated the effect of HMG when used in combination with human growth hormone [88].

Three of the reviewed RCTs addressed the use of insulin sensitizers (metformin and rosiglitazone) alone and as adjunct therapy to CC [94, 111, 112].

Pregnancy/gestation (pre-clinical, clinical, or ongoing) was expressed as overall number of pregnancies achieved per group, as pregnancy/fecundity rate (per patient, or per initiated, or per treated cycle) as a cumulative pregnancy over a time period or over a number of cyles (see Tables 3 and 4, Appendix E). However, pregnancy was clearly defined as one of the main outcome of interest only in four trials [68, 108, 109, 111]. The method used to diagnose or detect pregnancy was stated or described two studies [86, 107].

Not all studies reported on the risks and complications associated with the OI drug therapies evaluated. Information on all adverse outcomes of interest (miscarriages/abortions, multiple pregnancy and OHSS) was provided only in three RCTs [54, 86, 88] (see Tables 3 and 4, Appendix E). Three RCTs [107, 109, 112] provided no information on any of the adverse outcomes of interest. The remaining RCTs [68, 75, 94, 108, 110, 114] provided information on one or two of these complications.

The findings reported by these studies are not comparable as their investigators took different approaches (see Tables 3 and 4, Appendix E):

- Studies used different inclusion/exclusion criteria (type and duration of infertility, PCOS definitions, CC-resistance definitions, BMI values, cut off values of endocrine characteristics, US features of polycystic ovaries, infertility work up and ways of performing measurements).
- Notably, the reproductive outcome measures used in these trials differed considerably. Studies used different ways of defining and reporting the reproductive outcomes of interest, criteria for confirmation of ovulation, tests and methods for pregnancy diagnosis, and timing of performing tests to confirm/determine ovulation and pregnancy.
- Some studies evaluated the use of OI drugs alone while others evaluated the use of adjuvant therapies (pre-treatment or co-treatment) to OI drugs.
- Studies used different drugs (in terms of brand names and manufacturers).
- Studies used different regimens/protocols in terms of timing and duration of administration, route of administration, dosages, ways of monitoring therapeutic effects (equipment used for US examination, biochemical assays, definition/criteria used for determination of ovarian response). Some protocols included hCG administration (and used various criteria for timing or withholding hCG administration) some did not.

Methodological quality of the reviewed RCTs

None of the included RCTs met all of the criteria used to judge their methodological quality (Table 1, Appendix B). The information provided in Table 4 (Appendix E) shows the extent to which these criteria were met in each study. In most cases insufficient or inadequate information was provided in the published report to enable judgement on the validity of the reported findings to be made.

In all trials participants were randomised but for three of them [54, 75, 110] the methods used for randomization and allocation concealment were not reported. Five studies used adequate methods of randomization and allocation concealment (random numbers tables [86, 108], computer randomization [68, 88] and central randomization [107]). Two studies used partially adequate methods (opaque envelopes [94, 111]). When stated, the timing of randomization was commonly at the beginning of the cycle.

Operator and assessor bias could not be ruled out for any of the studies reviewed. None of the RCTs provided details on who administered the entire OI therapy. Neither does any RCT provide details on who measured and assessed the various outcomes. One RCT [68] mentiones that some injections were administered by one of the authors but gives no informarion about who administered the other injections or about who measured/assessed the outcomes.

Blinding was performed only in three RCTs [88, 94, 109]. In the study by **Homburg et al.** [88], blinding of patients and the person assigning treatment was performed but the method of allocation concealment was not reported. **Parsanezhad et al.** [109] provided no description of blinding (whether it was for investigators, patients or both). In another RCT [94] the investigators, patients and study personnel were blinded to their assignments. None of these studies provided details on how blinding was performed. Neither did any of these RCTs assess the adequacy of the blinding performed. Thus, it was impossible to judge its effectiveness, which might have been inadequate.

Of all reviewed RCTS, eleven were single centre trials [54, 68, 75, 86, 88, 94, 108, 109, 110, 111, 112] and one was a multicenter-trial [107]. Only five trials [75, 94, 108, 107, 109, 111, 112] clearly stated their setting (facility where the trial took place). The duration and time of the trial was mentioned in two trials [111, 112]. All trials used parallel design.

The majority of studies had small sample sizes, recruiting and including less than 50 participants [54, 68, 75, 86, 88, 94, 107]. Chance variation could not be ruled out. In only two studies [68, 94] a power calculation was performed and some details provided. No trials clearly identified the source population for their subjects and how they were recruited. The criteria for inclusion/exclusion of participants were defined in detail in five studies [68, 94, 107, 109, 111, 112]. Insufficient and inadequate information on these methodological aspects in most studies made it difficult to judge how appropriate the selection was for the participants the study was designed to assess.

Most of the RCTs did not specifically state whether they followed or not the intention-to-treat principle (see Table 4, Appendix E). The OI drug therapy protocols were defined and described adequately in most studies (see Table 3, Appendix E). For most trials the follow-up period was not clear.

Findings reported by the reviewed RCTs

CC therapy

No RCT conducted to evaluate the safety and efficacy of using CC or other anti-estrogen agent alone specifically to mange anovulatory infertility associated PCOS in women of reproductive age has been located through the present review's literature search.

One RCT[107] compared endocrine changes in 30 women treated either with pulsatile GnRH after pre-treatment with GnRHa (agonist) or with CC alone. No endocrine differences were found between groups. No statistically significant differences were reported between groups in terms of pregnancy rates per initiated cycle or in terms of delivery rates per pregnant patient. No statements were available on adverse outcomes of interest. The investigators considered that the "presumed clinical benefits" of using GnRH (after GnRHa) as compared to CC alone in these patients could not be demonstrated possibly due to the small sample size of their study.

One RCT[108] was conducted on the use of kenocotazole as an adjuvant to CC therapy in 97 women with insulin resistance. The group receiving kenocotazole had a higher incidence of monofollicular response and a higher rate of pregnancy per patient than the group who had only CC and had no abortions after cord pulse. The investigators concluded that the use of kenocotazole might improve responsiveness to CC and diminish its troublesome "biological effects". Because of insufficient information on patients' characteristics, it is not clear what subgroup of infertile women with PCOS and insulin resistance these results might be applied to.

Parsanezhad et al.[109] evaluated the effects of administering bromocriptine combined with CC in CC-resistant women with PCOS and normal prolactin (PRL) levels. The investigators found no significant differences in ovulation and pregnancy rates between treatment (bromocriptine+CC) and placebo (placebo+CC) groups. They concluded "that 10%-15% of patients with PCOS experienced occasional ovulatory cycles and pregnancy whether or not they were on treatment".

Gonadotrophin therapy

The literature search did not locate any RCT evaluating the use of gonadotrophins as the first line therapy in managing anovulatory infertility associated with PCOS in women of reproductive age. Located were six RCTs which evaluated various gonadotrophin preprations when used alone (in different regimens) or in combination with adjuvant agents to manage this type of infertility in women who failed to ovulate or conceive after CC.

The attempt to prevent multifollicular development following OI using gonadotrophin preparations in these women has given rise to a variety of different regimens of various types of gonadotrophin preprations. **Hugues et al.** [110] compared the safety and effectiveness of two low dose regimens of uFSH (step-up vs. sequential step-up and step-down) in 56 women. The sequential step-up and step-down protocol was found to to be "a safe and effective regimen" for these patients. The investigators concluded that decreasing the dose of uFSH after step-up follicular selection "may be an alternative method to avoid multifollicular development". There were no statistically significant differences in terms of pregnancies (clinical or ongoing) between groups. No statement was provided on whether any multiple pregnancies occurred in either group.

GnRHa has been utilized in conjunction with gonadotrophins also with the aim to reduce the multifollicular development in these women. According to the evidence reported by **Ergur et al.** [86], usage of GnRHa in conjunction with HMG has not decreased multifollicular development or the total gonadotrophin dose per cycle in these women when compared to the use of low dose HMG alone. The investigators found no statistically significant differences in the pregnancy rates (per patient and per cycle) or in the delivery rates between groups. Based on their results they advocated the use of "low-dose gonadotrophin therapy to prevent OHSS and multiple pregnancies".

Vegetti et al. [68] evaluated the effect of using a 3-month GnRHa in one cycle of OI with low dose pure uFSH in 20 women. Results showed no improvement with pre-treatment using GnRHa therapy in terms of ovulation and pregnancy rates. Lower ovulation and pregancy rates were reported in the group treated with GnRHa plus low-dose pure FSH compared to those in the group treated with low-dose pure FSH alone. The study was interrupted.

The study by **Lidor et al.** [75] evaluated the efficacy of GnRHa (agonist preparation) in preventing premature luteinization in 22 women. The use of GnRHa before FSH resulted in a decrease in the incidence of premature luteinization and improved fecundity. Four singleton pregnancies occurred in the group pre-treated with GnRHa vs. no pregnancies in the group treated with FSH alone. Based on these results, the investigators suggested that the avoidance of premature luteinization by using GnRHa may significantly improve fecundity in treated women. No statement was provided on the effect of using GnRHa on the incidence of miscarriages.

Muriana et al. [54] compared the use of a combination of an oral contraceptive (OC) agent and short term GnRHa vs. the use of depot GnRH in 30 women (control group). Both regimens gave similar pregnancy and delivery rates. No differences were observed in terms of incidence of abortions or OHSS cases between treatments. However, in the control group there were reported 2 sets of triplets and 1 set of twins as compared to two sets of twins reported for the group treated with OC/short-term GnRHa.

The effect of co-treatment with recombinant human growth hormone, GnRHa (agonist preparation) and HMG for OI was explored by **Homburg et al.** [88]. Their results suggested that adjuvant growth hormone treatment to GnRHa/HMG does not influence follicular development or sensitivity in response to gonadotrophins, and it does not seem likely to be of any potential clinical benefit (in terms of ovulation and pregnancy) rates for the treatment of PCOS.

The small sample size and the other potential limitations of the study design used (see Tables 3 and 4, Appendix E) do not permit generalization of these RCTs' findings. The reported results do not clearly demonstrate clinically significant differences in pregnancy rates between the various regimens evaluated. Patients' complication profiles were not adequately described.

Insulin-sensitizers

This review's literature search did not locate any RCT conducted on insulin sensitizers when used alone as initial therapy to achieve pregnancy in women with anovulatory infertility associated with PCOS.

George et al. [111] conducted an RCT to determine whether sequential treatment with metformin and CC would be as effective as treatment with HMG alone in improving ovulation and pregnancy rates in CC-resistant women with PCOS. In group I (metformin-CC) there was a significant improvement in ovulation after treatment (46.7%, $P < 0.001$). The ovulation rate in group II (HMG alone) was 43.3%, with a high drop-out rate. The investigators reported no significant difference in pregnancy rates between the two groups (five pregnancies in group I vs. seven pregnancies in group II). One woman in group I conceived during the 6-month pre-treatment with metformin. There were two normal deliveries in group I and six normal deliveries in group II, with more complications (one ectopic pregnancy and one intrauterine death) in group I.

A cost-effectiveness analysis showed the cost for medications per pregnancy was US$ 71 ± 3 in group I versus US$ 277 ± 171 in group II [111]. The investigators concluded that sequential treatment with metformin and CC is an effective and safe option for CC-resistant women with PCOS. They suggested it as a viable interim option for young women (<35 years of age) and a valuable treatment alternative for those who have financial constraints that preclude OI with HMG.

Ramzy et al. [112] investigated the potential value of metformin prior to and concomitent with the use of CC and its impact on improving ovulation rate and regularity of the cycle in both overweight and lean women with PCOS. The reported results showed no improvement in regularity of the cycles or ovulation in women on metformin alone compared to those who took placebo. However, the investigators observed a significant improvement in both lean and overweight women who took metformin and CC. No conception has occurred in any group. These results suggest that metformin intake prior and as adjuvant to CC has a clinical benefit in terms of improved ovulation rates in both lean and overweight women with PCOS. The intake of combined metformin and CC appears more efficacious in terms of ovulation rate than treatment with either drug alone.

Ghazeeri et al. [94] investigated the effect of rosiglitazone on inducing ovulation in overweight and obese CC-resistant women with clinical manifestations of PCOS. Overall, 14 of 25 (56%) women successfully ovulated. In Group I (rosiglitazone alone), four of 12 (33%) subjects ovulated compared with 10 of 13 (77%) women randomized to receive rosiglitazone and CC (Group II) (P=0.04, Fisher's exact). There was one pregnancy in Group I, resulting in one "uncomplicated live birth. Two women conceived in Group II, resulting in one "successful live births" and one spontaneous abortion. The investigators concluded that short-term rosiglitazone intake enhances both spontaneous and CC-induced ovulation in overweight and obese women with PCOS.

Although there was variation in the patients included in these three RCTs and the methods of assessment used, their reported results showed a consistent improvement in ovarian function. The results showed improvement in ovulatory response but the efficacy in achieving pregnancy following therapy with any of the assessed agents in infertile women with PCOS remains to be determined. All studies reported on achieving pregnancy as a result of treatment, but only one study [111] had pregnancy clearly defined as a main outcome. Gazheeri et al. [94] did not control for other causes of infertility. Patients' complication profiles were not adequately described.

Secondary research studies

The literature search revealed eighteen reviews of studies addressing the use of OI drug therapy in anovulatory infertility (both WHO group 1 and group 2). However, only six systematic reviews [59, 113, 114, 115, 116, 117] met the selection criteria described in Appendix A. Main characteristics of the selected systematic reviews and their main findings and conclusions are summarized in Table 5, Appendix E. Reasons for exlusion of the other twelve reviews are outlined in Table 2, in Appendix C.

None of the selected systematic reviews assessed the efficacy of ***CC therapy*** alone in terms of achieving pregnancy in anovulatory women with PCOS. A Cochrane Review evaluated the use of CC therapy alone for OI in women with oligo-menorrhea (WHO group 1 and group 2) [29]. None of their reviewed studies did specifically evaluate the safety and efficacy of using CC to achieve pregnancy in infertile women with anovulation and PCOS [29]. This Cochrane Review was excluded from the present review (see Table 2, Appendix C).

Four of the selected systematic reviews addressed the use of ***gonadotrophin therapy*** in in anovulatory women with PCOS [59, 113, 114, 116]. Cochrane Review Groups conducted [116] three of these reviews [59, 113, 114] and the fourth one was based on a Cochrane Review [116]. The use of uFSH versus HMG and the use of GnRHa as an adjunct to gonadotropin therapy in women with PCOS trying to conceive were assessed in one review [59]. Two reviews assessed the evidence on using GnRH for OI and the use of rFSH versus uFSH for CC-resistant PCOS patients trying to conceive [113]. Another review [114] compared the use of laparoscopic ovarian drilling with CC therapy; gonadotrophin therapy with or without GnRHa pre-treatment; a combination of either post-surgical CC or gonadotrophins compared with gonadotrophins alone; and various drilling modalities in women with CC–resistant PCOS.

The objectives of these reviews [59, 113, 114, 116] were to determine the safety and effectiveness of the above mentioned treatment modalities in terms of ovulation induction, pregnancy, miscarriage, multiple pregnancy and OHSS. According to these reviews:

- Tentative conclusions, based on a limited amount of data, suggest that despite theoretical advantages uFSH preparations did not improve pregnancy rates in women with PCOS when compared to traditional and cheaper HMG preparations [59]. The only demonstrable benefit was a reduced risk of OHSS in cycles when administered without GnRHa. The routine addition of GnRHa to gonadotrophins is unjustified at present. Due to insufficient data, no conclusions could be drawn on miscarriage and multiple pregnancy rates [59].
- As yet, there is insufficient evidence to conclude that OI using rFSH is safer and more effective in achieveing clinical pregnancy than OI using uFSH for women with CC-resistant PCOS [116].
- The available evidence on the use of pulsatile GnRH in women with CC-resistent PCOS is not sufficient to either prove or discard the value of this therapy for this indication [113].
- There is insufficient evidence of clear superiority of one over the other in terms of ongoing pregnancy. The laparoscopic ovarian drilling "may be the treatment of choice since the avoidance of gonadotrophins may reduce the risk of multiple pregnancy and ovarian hyperstimulation syndrome" [114].
- In the absence of any direct comparison, laparoscopic drilling cannot be recommended in preference to clomiphene as a primary form of treatment for women with anovulatory PCOS [114].

Two systematic reviews addressed the use of ***insulin sensitizers***, alone or in combination with other OI therapies, in anovulatory women with PCOS [115, 117]. One of these studies [115], conducted by a Cochrane Review Group, assessed the safety and effectiveness of various insulin sensitizers. Based on their findings the reviewers concluded that metformin is effective for anovulation in women with PCOS when used either alone or in combination with CC [115]. The combination of metformin with CC may result in higher ovulation rates, particularly in women known to be previously CC-resistant. However, they reviewers caution that the evidence suggesting a significant effect on pregnancy rate for metformin combined with CC should be interpreted with care. There is no evidence to indicate whether there is an increased multiple pregnancy rate following the combination of metformin and CC. There are no safety data on its long-term use in young women.

The other systematic review [117] assessed the effectiveness of metformin in anovulatory women with PCOS. The reviewers concluded that limited data on mainly obese women suggested that metformin alone improves both restoration of regular menses and spontaneous ovulation [117]. There are no data to suggest an improvement in pregnancy rate following therapy with metformin alone in women with PCOS. The combination of metfomin and CC results in an improved ovulation and pregnancy rate in both unselected and CC-resistant PCOS women.

Four review groups concluded that further RCTs with sufficient power and of better methodological quality were required to substantiate some of their findings with more confidence and determine the clinical role of the evaluated therapies for this indication [59, 114, 116, 117].

DISCUSSION

Anovulatory infertility is associated with PCOS in the majority of reproductive-aged women. PCOS is still an enigmatic condition, characterized by many heterogenous clinical and endocrine features. Its definition and the exact criteria necessary for an accurate and differential diagnosis remain an area of considerable debate. Consequently, the safest and most effective therapy in terms of achieving pregnancy in these women is still a matter of controversy.

Currently, OI drug therapy is the predominant intervention used for managing anovulatory infertility associated with PCOS. However, findings from the RCTs included in the present review did not show any of the evaluated therapies as superior to another in terms of safety and effectiveness in achieving pregnancy for this indication.

This review's findings are consistent with those reported by previous ones [16, 59, 113, 114, 115, 116, 117] regarding the limited availability of reliable data on the use of various approaches to OI drug therapy. None of the RCTs included in this review dealt with the same comparisons, all were small to moderate size and their methodological quality was limited. Their conclusions remain tentative as they were based on limited data. Further RCTs of larger sample sizes and better methodological quality (which should attempt to overcome the limitations of the reviewed studies) are needed to substantiate their conclusions.

First line option

Lifestyle modification has been suggested as the first line of therapy to induce ovulation in these women before starting OI drug therapy. Change of weight is recommended in women who are overweight or underweight to ameliorate the metabolic consequences of PCOS and improve response in terms of achieving pregnancy [13, 14].

The CC therapy has been and continues to be recommended as the first line option for OI drug therapy to manage anovulatory infertility in women of reproductive age. This choice is based on its relative safety (mild side effects and no marked OHSS), high effectiveness in achieving ovulation, simple mode of administration (orally), no requirement for close and frequent monitoring, and relatively low cost.

However, in infertile women with PCOS, only about half of those who successfully ovulate following CC therapy also achieve pregnancy. Also its use carries an increased risk of developing multiple pregnancies. This review confirms findings reported by previous ones that there are insufficient reliable data on the safety and efficacy of using CC therapy alone to manage anovulatory infertility in women with PCOS [17, 29].

The use of CC therapy is considered to be safe based on the experience gained with it in the last 40 years. There are however, several reports indicating an alteration in the sex ratio of children at birth that has not been noted with HMG [101, 103]. CC has been shown to reduce this ratio and result in fewer males at birth. The size of the reported effect from a meta-analysis of available studies will be difficult to confirm in anything but the most rigorous follow-up study [101]. Currently, properly designed follow-up studies are lacking.

No evidence published on use of OI with gonadotrophin preparations alone as first line therapy over CC in the management of anovulatory infertility in women with PCOS has been located. Clinical reviews, discussions and commentaries on this topic suggest that, compared to CC therapy, the gonadotrophins have a higher rate of multiple gestations and are more likely to lead to OHSS. Gonadotrophin therapy is also more complex and resource intensive, requires specialized careful and frequent monitoring, and is more expensive. Recombinant FSH preparations appear to be the most expensive [19].

Options for CC-resistant women

The most frequently advocated medications for women unresponsive to standard or modified therapies with CC are various regimens of gonadotrophin preprations, with or without GnRHa. Many of the reviewed studies [54, 59, 68, 75, 86, 110, 113, 116] addressed issues referring to whether any gonadotrophin preparation is superior to another, whether low dose regimens are superior to standard/conventional dose regimens, the role of using GnRH, the role of using GnRHa in addition to gonadotrophins, and which method best limits the risks and complications associated with the use of gonadotrophins.

Currently, there are three types of gonadotrophin preparations: HMG, uFSH, or rFSH. The systematic reviews conducted on the use of these preparations tentatively concluded that there is no definitive evidence to confirm higher pregnancy rates with the use of one preparation compared with another in infertile women with PCOS [59, 116]. There was no definitive answer on which method best limits the increased risk of multifollicular development and miscarriages in these women. However, comparisons of uFSH and HMG suggested a lower incidence of OHSS following uFSH [59].

The dose used appears to be much more important than the preparations used. Results from two RCTs [86, 110] suggested that low dose regimens (regardless of the preparations used) may be considered in this population in order to reduce the risk of multifollicle development. However, low dose gonadotrophin therapy may still lead to multiple follicular development and does not appear to improve pregnancy rates in these women. Excess body weight and insulin resistance appear to adversely influence pregnancy rate following this therapy [5, 48].

The results from one RCT[107] and one Cochrane systematic review[113] suggest that the role of using pulsatile GnRH in the management of infertile women with PCOS (with or without CC-resistance) is yet to be defined. Currently, there is insufficient scientific evidence on its efficacy/effectiveness for this indication to either prove or disprove its value. It has been suggested that factors such as obesity, hyperinsulinemia, hyperandrogenism and LH hypersectretion may be adversely affecting the treatment and markedly reduce its efficacy[31, 39, 52, 55].

Adjunct therapies

To improve responsiveness to CC in this population, some investigators used ketoconazole (an anti-androgen) as an adjunct therapy to CC[108]. Results reported by one RCT[108] are encouraging but the side effects of this drug may limit its use for infertility treatments. Ketoconazole is best known for its anti-fungal actions[25, 108]. A serious side effect of this agent is hepatic toxicity, in rare cases leading to death[25].

The combination of bromocriptine and CC therapy was also proposed and its use in CC-resistent women with PCOS and normal prolactin levels was studied in one RCT[109]. The results indicated no clinical utility in terms of ovulation and pregnancy rate.

Evidence from four RCTs[54, 68, 75, 86] and one Cochrane Review[59] suggests that the routine use of GnRHa as an adjunct to gonadotrophin therapy is not justified in these women. Although adjuvant GnRHa has been reported to decrease the rate of premature luteinization[75], its clinical utility in terms of improving rates of pregnancy and reducing risks and complications associated with the use of gonadotrophin therapy has yet to be established.

According to the results reported by one small RCT[88], the clinical benefit of using human growth hormone as an adjunct to gonadotrophin therapy using HMG preparation with the aim to improve responsiveness in CC- resistant has yet to be detemined.

Emerging approaches

New approaches for OI drug therapy for the management of anovulatory infertility associated with PCOS (with or without CC resistance) are still emerging. Recently there has been an increased interest in the use of insulin sensitizing agents to reduce insulin resistance and address the ovulation problems associated with it. Among all agents available on the market, metformin has been studied in most detail in this population and has been shown to be promising. However, its role in the management of this condition is still to be determined.

Evidence obtained from two RCTs[111, 112] and two systematic reviews[115, 117] suggest that metformin may be beneficial as an adjunct to CC in women with PCOS, in terms of both ovulation and pregnancy rates. However, its efficacy in achieving pregnancy has not been clearly demonstrated and long-term data on its safety is lacking. Also, there is insufficient evidence to limit the use of metformin to a specific sub-group of patients.

The use of metformin was associated with dose-related gastrointestinal side effects which limited participation levels in the reviewed studies and may limit the patient's compliance. Currently, it remains unclear which dose and combinations of metformin and CC are optimal in treating these women.

Rosiglitazone, which appears not to be associated with the gastrointestinal disturbances commonly reported with metformin, has been shown promising in improving ovulation in overweight and obese women with PCOS in one small RCT [94]. However, the reported results did not demonstrate significant effect in terms of achieving pregnancy in these women. Its liver safety profile has yet to be fully determined [94, 115, 118].

Risks and complications

Prior to treatment, the side effects of the OI drug therapy and the potential for developing complications for both the mother and child should be outlined. Infertile women with anovulation and polycystic ovaries appear to be at an increased risk of developing serious complications following OI drug therapy. The use of OI agents in these women may result in unpredictable numbers of follicles and they are at an increased risk of developing multiple pregnancy and OHSS. There is also evidence to suggest that women with PCOS may be at an increased risk for complications during pregnancy (i.e., gestational diabetes, pregnancy-induced hypertension, problems associated with delivery and low-birth-weight infants) [4, 9, 32, 45, 46, 49].

The couples must be made aware that among all options, gonadotrophin therapy is a major cause of multiple pregnancies and births, especially high order ones that are associated with considerable human and financial costs [50, 60, 119, 120, 121], (http://www.asrm.org).

OHSS occurs more commonly following gonadotropin therapy. Overall, the potential for developing severe OHSS is increased in OI protocols that utilize relatively high doses of gonadotrophins [9, 19, 23, 28, 60, 81, 122] (http://www.asrm.org).

Appropriate selection of patients, various modifications of the treatment protocol, effective and strict monitoring during treatment and withholding hCG injections can reduce the incidence of these serious complications [9, 23, 18, 19, 28, 55, 58, 60, 61, 81, 122, 123]. However, the risk cannot be entirely removed or prevented when gonadotrophins are administered. Careful and frequent monitoring is required, particularly when gonadotrophin therapy is used, which may be expensive and labour intensive.

Although, the timing and withholding of hCG administration are very important to avoid serious complications following gonadotrophin therapy, it is not clear what criteria to use. In the reviewed RCTs, the investigators used various criteria in terms of mean diameter of the dominant follicle and number of follicles and various monitoring means.

Women with PCOS appear to be at a higher risk for spontaneous abortions or miscarriages. Approximately one-third of all women with PCOS who become pregnant experience spontaneous abortion/miscarriage [2, 31, 32, 53]. Increased BMI and hypersecretion of LH have been associated with these increased risks [5, 14, 21, 31, 34, 38, 39, 53]. However, the reasons for this are still unclear.

The eligible candidates also need to be aware of the potential increased risk of developing ovarian cancer following prolonged use of OI drugs. Although to date no convincing data exist regarding this potential association, the careful use of the OI drugs is recommended.

Some evidence suggests that among infertile women, those with anovulation and PCOS have an increased risk of developing endometrial cancer, breast cancer or ovarian cancer [124]. Data analyses based on a small number of patients, suggest a relationship between this risk and the disturbed gonadotrophin concentrations and ratios that exist in these women. The reasons for this are still unclear.

Definition problems

The existence of various subgroups of PCOS-like conditions increases the challenges for management of anovulatory infertility in these women. Regimens found to be useful in one subgroup may not be equally applicable to others. The different definitions and criteria used to diagnose PCOS emphasize different aspects of the syndrome and this could also result in varying responses to a particular OI drug therapy.

The reviewed literature suggests that sub-classification of infertile women with PCOS is essential in the selection of the safest and most effective OI drug therapy. However, selection criteria for treatment are not available. Current knowledge provides limited direction on the adoption of a treatment-oriented classification for sub-groups of these women. No clinical and/or endocrinological parameters allow for the separation of hyper-responders from hypo-responders to OI drug therapy.

Also, CC-resistance is poorly understood and defined [12, 21, 26, 39, 49, 52, 53, 55]. Some investigators consider CC-resistance to mean failure to ovulate (no response), others take it to mean failure to conceive despite ovulation or take it to mean either. This definition problem causes confusion when it comes to comparing pregnancy rates obtained with various approaches to OI drug therapy.

Implications for clinical practice

Those offering and considering OI drug therapy to manage anovulatory infertility associated with PCOS should be aware that:

- For overweight or obese women weight loss is recommended before initiation of OI drug therapy, to ameliorate the metabolic consequences of PCOS and improve response. A principal consideration is how to better assist these women to reduce their weight.
- CC therapy remains the first choice for potential candidates for OI drug therapy. However, success in achieving ovulation equates with success in achieving pregnancy only in 40%-50% of cases. An increased risk of developing multiple pregnancy following CC therapy should be considered.
- For women not responsive to CC (failed to ovulate or conceive after CC) the therapeutic options most frequently advocated are either OI with various regimens using gonadotrophins or laparoscopic ovarian drilling [114]. Currently, there is insufficient evidence of clear superiority of one over the other and criteria for selecting women who would benefit most from any of these therapies are not available. Laparoscopic drilling may be difficult to perform in obese patients, for whom complication rates are likely to be higher than in slimmer patients undergoing laparoscopy [13,] (Cumming, personal communication).
- It is still not certain whether any type of gonadotrophin preparations currently available is superior in improving pregnancy rates and reducing complication rates when used for this indication. Low-dose regimens (regardless of gonadotrophin preparations) may be considered in order to reduce the risk for multiple follicle development and the associated complications.
- For selected cases (women who are obese and/or hyperinsulinemic), the use of metformin as a pre-treatment and then in combination with CC improves ovulatory response and appears to increase chances of achieving pregnancy. However, metformin is not licensed for this indication. Data regarding its use alone or as an adjuvant therapy remain to be confirmed before recommending it as a standard therapy.
- OI therapy using pulsatile GnRH is less likely to be effective in these women.
- There is no clinical advantage in the routine use of GnRHa in addition to gonadotrophin therapy for this indication.
- The exact relationship and the roles of other adjuncts used in addition to CC therapy or to gonadotrophin therapy for this indication have not been fully elucidated.

Prior to treatment, potential candidates for OI drug therapy should be made aware that:

- regardless of the specific drug used, they appear to be at increased risk for multifollicular development and spontaneous abortion;
- the risk of developing serious complications such as multiple pregnancies and ovarian hyperstimulation syndrome appears to be higher when gonadotrophin therapy is used; and
- there may be a reduced probability of a male birth following CC therapy.

Appropriate care for these women requires careful use of the agent considered, close monitoring for adverse events, and long-term follow-up. To maximize the reproductive outcome and minimize the risk for complications associated with multiple follicle development in treated women, the OI drug therapy (particularly when using gonadotrophins) should be undertaken only by reproductive specialists with appropriate expertise in centers that allow access to same day estradiol measurements and ultrasound monitoring.

Implications for future research

The choice of the safest and most effective OI drug therapy for anovulatory infertility associated with PCOS depends on the individual circumstances of each particular case, and appropriate patient selection is critical to achieving pregnancy. Further research for an accurate and detailed sub-classification of women with PCOS is warranted as it may have important therapeutic implications for the management of anovulatory infertility in this population.

Many questions remain unanswered as to the role of various approaches to OI drug therapy in managing anovulatory infertility associated with PCOS. Well-designed and conducted RCTs on the use of these modalities for longer time are needed to provide definitive evidence on their value in managing anovulatory infertility associated with PCOS.

Cost data are needed to aid in the women/couple's decision-making and to assist in the formulation of public policy and research policy for management of this indication.

CONCLUSIONS

Infertile women with anovulation and PCOS appear to be one of the most difficult groups to treat safely and successfully with OI drug therapy. The aim of using OI drug therapy in these women is to correct infertility problems associated with PCOS and to enable the delivery of a single, normal, healthy child. However, PCOS represents a heterogeneous condition in terms of phenotype, endocrine abnormalities and response to OI drug therapy.

The OI agents currently in use do not benefit all women with anovulatory infertility associated with PCOS willing to conceive and can pose serious health risks if used inappropriately. Part of the difficulty in managing this condition is that there is no universal definition of the syndrome and no generally agreed upon criteria for diagnosing it.

The findings outlined by this review confirm those reported by the Canadian Royal Commission that the issues related to using OI drug therapies still need further consideration. OI drug therapy appears to be effective in achieving pregnancy in this population, but there is insufficient evidence to allow firm conclusions on which agent is the safest and the most effective. There are only few RCTs (of small sample size, short duration, and limited methodology) of any OI drug therapy in anovulatory infertility associated with PCOS. The clinical significance of their reported results has yet to be established.

The available evidence does not provide clear treatment guidelines. CC therapy remains the most effective and economic one in women with PCOS in terms of ovulation rates. Half of women who achieve ovulation in response to CC therapy also conceive. For women who fail to ovulate or conceive following CC therapy, gonadotrophin therapy appears to be the next medication of choice.

The use of both CC therapy and gonadotrophin therapy is associated with increased risk of multiple follicle development in these women. The risk of developing complications such as multiple pregnancies and OHSS appears to be higher when gonadotrophins are used. Low dose regimens (regardless of gonadotrophin preparations) may be considered to reduce the risk of developing serious complications.

Pre-treatment and adjuvant therapy with metformin appears to increase the likelihood of response to CC and has been proposed as a sequential therapy before the use of gonadotrophins. However, its efficacy in achieving pregnancy in this population and long-term safety are still to be determined.

Prior to treatment, potential candidates for OI drug therapy should be given information about their chances of success in achieving pregnancy and that they may be at increased risk of developing serious complications.

The long-term effects of OI drug therapy on both mothers and their children are yet to be established. The follow-up periods in the reviewed RCTs were short and many more years of monitoring are required for the assessment of safety and efficacy of the assessed approaches. It would be desirable for a registry to report cycle-specific data and information on short- and long-term outcomes following OI drug therapy as used in Canada. Such an approach would provide more realistic measures of success obtained with various approaches and of the outcomes for treated women and their children.

APPENDICES

APPENDIX A: METHODOLOGY

The initial aim of this assessment was to determine what was in the published literature about the safety and efficacy/effectiveness of OI drug therapy used alone to manage anovulatory infertility of any type and achieve pregnancy in women of reproductive age. However, after a preliminary review of all citations and papers retrieved, only articles published on the use of OI drug therapy for anovulatory infertility associated with PCOS were selected. According to the reviewed published literature, OI drug therapy is primarily indicated for women of reproductive age with amenorrhea and oligomenorrhea. PCOS represents a common disorder in reproductive-aged women with these conditions and is the most common cause of anovulatory infertility in this age group.

Literature search

A systematic and comprehensive search was performed to identify relevant information and scientific evidence on the topic. The sources searched, the time limits and keywords used, and the number of citations found were as follows:

Database	Platform	Edition	Search Terms[†]
Cochrane Library Cochrane Database of Systematic Reviews	WWW	Issue 3, 2003	(((ovulat* OR ovar*) AND (stimulat* OR induct*)) AND (anovulat* OR polycyst*)) = 28 systematic reviews = 9 protocols
Cochrane Library The Cochrane Central Register of Controlled Trials (CENTRAL)	WWW	Issue 3, 2003	((((ovulat* NEXT induct*) OR (ovar* NEXTstimulat*)) AND (anovulat* OR polycyst*)) AND random*) = 60 citations
CINAHL	Ovid	January 1993 to October 2003, (Week 1),	exp Ovulation induction AND (exp Polycystic ovary syndrome OR exp Anovulation OR exp Ovarian cysts) = 7 citations
CRD Databases (DARE, NHS EED)	WWW	Searched 2003/10/09	((ovulat AND induct) OR (ovar AND stimulat)) AND (polycyst OR anovulat) DARE= 8 citations NHS Economic Evaluation Database (NHS EED) = 3 citations
CRD Databases (HTA Database)	WWW	Searched 2003/10/09	(ovulat AND induct) OR (ovar AND stimulat) HTA = 5 citations

Database	Platform	Edition	Search Terms[†]
EBM Reviews - ACP Journal Club	Ovid	January 1991 to July/August 2003	((ovulat$ or ovar$) and (stimulat$ or induct$) and (anovulat$ or polycyst$)).mp. = 0 citations
ECRI	WWW	Searched (for update) 05/08/03	(ovarian AND stimulation) OR (ovulation AND induction) OR ovulation induction OR ovarian stimulation = 9 citations
EMBASE	Ovid	January 1993 to 2003 (Week 40)	exp Ovulation induction AND (exp Polycystic ovary syndrome OR exp Anovulation OR exp Ovarian cysts) AND "randomized controlled trial" =36 citations
HealthSTAR/Ovid Healthstar	Ovid	January 1993 to August 2003	exp Ovulation induction AND (exp Polycystic ovary syndrome OR exp Anovulation OR exp Ovarian cysts) =0 citations
International Pharmaceutical Abstracts	Ovid	January 1970 to September 2003	((ovulat$ OR ovar$).mp. AND (stimulat$ OR induct$).mp.) AND (anovulat$.mp. OR polycyst$.mp.) AND random$.mp. =1 citation
Medline	Ovid	January 1993 to October Week 1 2003	exp Ovulation induction AND (exp Polycystic ovary syndrome OR exp Anovulation OR exp Ovarian cysts) limit to randomized controlled trial limit to human = 36 citations
PubMed	WWW	Searched 2003/10/09	((ovulation induction OR ovarian stimulation) AND (anovulation OR anovulat* OR ovarian cysts OR polycystic ovary syndrome OR polycyst*)) AND (randomized OR randomised OR randomly OR random OR ((double [WORD] AND blind* [WORD]) OR placebo [WORD])) NOT (animal) OR ((ovulation induction OR ovarian stimulation) AND (anovulation OR anovulat* OR ovarian cysts OR polycystic ovary syndrome OR polycyst*)) AND systematic[sb] = 118 citations

Database	Platform	Edition	Search Terms†
Science Citation Index	Web of Science	Searched 2003/10/09	((ovulation induction) OR (ovarian stimulation)) AND polycyst* AND (random*) = 51 citations
CMA Clinical Practice Guidelines Infobase	WWW	Searched 2003/10/06	ovulation induction = 1 citation
National Guideline Clearinghouse	WWW	Searched 2003/10/07	(ovarian stimulation OR ovulation induction) AND polycystic = 3 citations

Note:

* is a truncation character that retrieves all possible suffix variations of the root word. In databases accessed via the Ovid platform the truncation character is $.

†Searches limited to English language.

Where such function is available, searches were also limited to:

- Publication dates: 1993 and on
- Human studies

The websites of the Health Ministries for the provinces of Alberta, Ontario, British Columbia and the website of Health Canada were searched, for information on regulatory status and coverage of various OI drug therapies in Canada, using the following keywords:

> gonadotrophin/gonadotropin releasing hormone or GnRH (leutinizing hormone releasing hormone (LHR-H)), Gonal-F (follitropin a), Follistim (follitropin b), Puregon (follitropin b), Gonadorelin (lutrepulse, Factrel), Goserelin (Zoladex), Leuprolide (Lupron), metformin, and rosiglitazone.

Other websites searched are listed below

Websites
www.mycabot.ca (Searched on 2003/10/09) ovulation induction or ovarian stimulation =0
WWW using Google to search the Aetna and BlueCross BlueShield websites =2 coverage bulletins
www.icsi.org (Searched on 2003/10/10) =0

Websites
US Medicare Coverage www.cms.gov/coverage (Searched on 2003/10/10) ovulation =1 document
WWW using Google to search for websites of specialized clinics and societies.

The subject headings and textwords were used alone or in combination to ensure a high recall rate of relevant citations.

The literature search was focused on studies/papers/articles published between 1993 (since the completion of the final report of the Royal Commission on New Reproductive Technologies) and October 2003. It was limited to English language publications on humans.

The reference lists of all articles retrieved were examined for other studies that could have been missed by the electronic searches.

Screening and reviewing the literature

Two reviewers (PC and AS) independently screened the titles and abstracts of all retrieved citations for potential relevance. Full papers, obtained for citations initially selected for retrieval, were then read independently by the same reviewers and assessed for inclusion. Papers not relevant to the subject in question and those not meeting the selection criteria were excluded. Any differences in opinion between the two reviewers were resolved by consensus meeting.

The selected primary quantitative research studies were reviewed and their methodolocal quality was critically appraised independently by two reviewers (PC and AS). Details of these and their reported results were extracted and summarized in tabular form (Table 3 in Appendix E) by one reviewer (PC).

The methodological quality of the selected primary research studies was considered in terms of the information provided in their published reports on trial design, population characteristics, details of interventions used, and the reporting of outcomes in the published report of each study. These criteria were formulated having regard to the evidence needed to confidently determine the efficacy of OI drug therapy when administered alone to treat anovulatory infertility and achieve pregnancy (Table 1, Appendix B). The evidence itself was not graded but it was synthesized using qualitative methods in Table 4 (Appendix E) and described narratively in the text.

Main conclusions from published reports of systematic reviews of the evidence on the use of OI drug therapy for this indication and details of their methodology are also summarized in tabular form (Table 5 in Appendix E). The methodological quality of these studies was not critically appraised and no attempt was made to assess the validity of their findings.

Selection of the material

From the references identified, a selection was made that included:

- RCTs or quasi-RCTs (with ≥ 10 subjects in each arm) conducted prospectively to evaluate the safety and efficacy of OI drug therapy for anovulatory infertility associated with PCOS as compared with another OI treatment, a placebo or no treatment; **if there were no published RCTs or they were not appropriate for this particular clinical question**, other primary quantitative studies (such as non-randomized controlled trials, cohort studies, case series or case reports) were not included in the critical appraisal;
- systematic reviews and critical appraisals conducted to evaluate the safety and effectiveness of OI drug therapy for anovulatory infertility associated with PCOS;
- previous HTA reports on the use of OI drug therapy to treat anovulatory infertility in women of reproductive age;
- guidelines, position papers, consensus statements, or minimum standards for the use of OI drug therapy for anovulatory infertility;
- clinical review/overview articles, commentaries and discussions presenting background information on anovulatory infertility, PCOS, and on anovulatory infertility associated with PCOS; and
- overview articles, commentaries and discussions presenting background information regarding risks and complications associated with and costs of using OI drug therapy for anovulatory infertility associated with PCOS.

After a preliminary scanning of all citations, mostly background articles published after 1997 were selected since many advances in the understanding of anovulatory infertility and PCOS, and new drug therapies and new work in the area of biochemistry of the OI agents occurred in the last 5 years. However, papers (presenting background information on the topic) published before 1997 were retrieved and quoted when appropriate.

For the purpose of this assessment, ***primary and secondary research studies were included*** for review ***if***:

- they reported on the use of OI drug therapy alone to manage anovulatory infertility associated with PCOS;

- they reported on the use of OI drug therapy in women of reproductive age (≥18 years); or
- they used conception, pregnancy, fecundity or fertility rates as outcome measures.

The published ***primary and secondary research studies were excluded*** from the review (see Table 2 of excluded studies in Appendix C) ***if***:

- they evaluated the use of OI drug therapy for other types of anovulatory infertility (i.e. infertility caused by hyperprolactinemic anovulation, and infertility caused by hypo- or hyper-gonadotrophic anovulation);
- they also included cases suffering from other types of anovulatory infertility (i.e. infertility caused by hyperprolactinemic anovulation, and infertility caused by hypo- or hyper-gonadotrophic anovulation) and did not report results separately;
- they evaluated the use of OI drug therapy for other types of infertility (such as infertility associated with endometriosis, unexplained fertility, and/or male infertility);
- they included cases with other types of infertility (i.e. infertility caused by endometriosis, male factor and/or infertility characterized as unexplained) and did not report results separately;
- they included cases with more than one cause of infertility (i.e. couples diagnosed with anovulatory infertility and infertility caused by male factor) and did not report results separately;
- they evaluated the use of OI drug therapy in women with infertility undergoing ARTs such as artificial insemination, IVF and variations of IVF (i.e. intra-cytoplasmic sperm injection or ICSI and gamete intra-Fallopian transfer or GIFT); or
- they included cases undergoing OI drug therapy in combination with other therapies or procedures (such as IUI, IVF or variations of IVF) and did not report results separately.

Quantitative and qualitative systematic reviews which did not describe their search strategy, review methodology and inclusion/exclusion criteria were ***excluded*** from this review.

Editorials, letters, and technical reports were also excluded.

APPENDIX B: CRITICAL APPRAISAL OF SELECTED PRIMARY RESEARCH STUDIES

The critical appraisal of the methodological quality of the RCTs included was performed using the criteria listed in Table 1.

Table 1: Criteria for determining methodological quality of selected RCTs

Symbol	Criterion
A	The study was well designed and conducted: --randomization method was stated (concealment of randomization) -- multicentre or single centre design --cross-over or parallel design --blinding was present or not --if trial was blinded, details/description on the procedures performed and how blinding was done were provided and assessment of the adequacy of blinding was done; --description of the sample size calculation was provided --information was provided on the number of withdrawals or drop-outs and reasons and these were handled appropriately in the analysis; possibility of attrition bias was discussed --study participants who crossed over between treatments (where applicable) were mentioned and handled appropriately in the analysis --information was provided on whether an 'intention to treat' analysis was done, not done but possible, not possible, or uncertain --information on compliance was provided and assessment of compliance was done and discussed --duration, timing and location (setting) of the trial were stated
B	Description of study population was adequate: --type of infertility (primary, secondary) and diagnostic category (definition/criteria used for PCOS; definition criteria used for CC-resistance where women with this characteristic were included); --baseline characteristics (age; BMI; parity; other/co-existing infertility causes; infertility work-up and diagnostic tests; previously administered treatment) -- other characteristics: definition and duration of pre-existing infertility; information on the male partner sperm parameters and tubal patency
C	Selection of study population was adequately described (to identify the source population for patients and how they were recruited) nclusion and exclusion criteria for subjects were described and clearly defined
D	Therapeutic regimen was defined and adequate description was provided (type of treatment; stimulation protocol; time of initiation; modality and frequency of administration; information on who administered the treatment; dose; adjustment criteria; co-interventions, completed participation, follow-up period)
E	Results were adequately reported: number of patients/cycles initially included or randomized, and excluded and analyzed; number of cycles/couple, single/separate reporting of outcomes by therapy and by diagnostic category/cause of infertility (where applicable); CI for the outcomes of interest were reported; statistical significance for the outcomes of interest was reported in terms of p-value, mean value and standard deviation (SD) or standard error (SE)
F	Complications were adequately reported (by diagnostic category and by procedure) and statements on the presence/absence of OHSS, multiple pregnancy, and miscarriage) were present in the published report
G	Implications for practice and research were discussed; study limitations were described; their impact on reported results was discussed.

These pre-determined criteria were developed according to an explicit methodology used and published by the University of Alberta accessed at http://www.med.ualberta.ca/ebm/ebm.htm. The assessment was performed taking into account the principles of the Cochrane Collaboration (http://www.cochrane.org/) and the material published on critical appraisal of the medical literature in the CRD report four (accessed at http://www2.york.ac.uk/inst/crd/report4.htm) and in peer reviewed journals such as British Medical Journal and Journal of the American Medical Association.

Conciliation of disagreements on the methodological quality of the studies reviewed and critically appraised was facilitated through and consensus was reached by discussions between the two assessors.

Note:

The assessment of the methodological quality of the reviewed RCTs was based on the information provided on methodological domains in the published reports of these studies. Additional information on trial methodology and/or actual original trial data were not sought by evaluation of research protocols and from the authors of trials that had unclear or inadequately described aspects of methodology, or reported data in a format unsuitable for extraction into a tabulated format.

APPENDIX C: STUDIES ON THE USE OF OI DRUG THERAPIES EXCLUDED FROM THIS ASSESSMENT/REVIEW

Table 2: Summary of the final exclusion process based on the full text article

Study	Study Type	Reason for Exclusion
RCOG [125]	Clinical guidelines	Provides recommendations which focus on the management of infertile couples having IVF and donor insemination in tertiary care
Collins and Hughes [15]	Systematic review	Did not describe their search strategy; it reported separately results for women classified in WHO group 1 and WHO group 2 and did not report separate results for PCOS cases.
Hughes et al. [29]	Systematic review	Included women with oligo-menorrhea (both WHO group 1 and WHO group 2) and did not report results separately for women with anovulatory infertility associated with PCOS.
Hughes et al. [87]	Systematic review	Included two studies (Bacchus et al. 1990 and Homburg et al. 1990) that had participants with additional sub-fertility diagnoses such as endometriosis, adhesions and oligospermia.
Hughes et al. [126]	Systematic review	Withdrawn from publication as it was superceded by a Cochrane Review (Nugents et al. [59]) on gonadotrophin therapy for ovulation induction in subfertility associated with PCOS.
Bayram et al. [127]	Systematic review	Included four RCTs which were also reviewed in a recent systematic review on the same topic (van Wely et al. [116]), which also reviewed extra RCTs and was included in this report.
Lord et al. [128]	Systematic review	This review is an edited version of a Cochrane Review (Lord et al. [115]) that was included in this report.
ECRI [58]	Executive Briefings	Did not describe their review methodology, search strategy and inclusion/exclusion criteria; it is an overview of all female infertility technologies, and does not report separately for women with anovulatory infertility associated with PCOS.
ECRI [7]	HTA report	Did not describe their review methodology, search strategy and inclusion/exclusion criteria; it is an overview of all female infertility technologies, and does not report separately for women with anovulatory infertility associated with PCOS.

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Table 2: Summary of the final exclusion process based on the full text article (cont'd)

Study	Study Type	Reason for Exclusion
Larizgoitia et al. [19]	HTA report	Did not describe their review methodology, and inclusion/exclusion criteria; included women classified in WHO group 2 and did not report results separately for women with PCOS.
Harborne et al. [93]	Descriptive review	This review summarized data from several RCTs reporting on the use of metformin in women with PCOS. It did not describe in detail the review methodology and the search strategy and selection criteria were not clearly presented. The RCTs included in this review were also reviewed in a quantitative systematic review (Lord et al. [115]), which also reviewed extra relevant RCTs and was included in this report.
Barbieri [91]	Review	The objective of this descriptive review was to review for the obstetrician-gynecologists the use of metfoming for treatment of PCOS as reported in randomized and non-randomized controlled trials. The review methodology was not described in detail and the search strategy and selection criteria were not clearly presented. The RCTs included in this review were also reviewed in a quantitative systematic review (Lord et al. [115]), which also reviewed extra relevant RCTs and was included in this report.
Haas et al. [92]	Review	This is a review of studies addressing biochemical and clinical changes in women with PCOS treated with metformin. The review methodology was not described.
Fridström et al. (1999) [67]	Randomised controlled trial	The comparator was IVF, which is ia an assisted reproductive technique not established as an OI therapy to manage anovulatory infertility associated with PCOS.
Hedon et al. (1998) [129]	Randomised controlled trial	Already analyzed in a systematic review (van Wely et al. [116]), which was included in this report.
International Recombinant rhCG Study Group (2001) [77]	Randomised controlled trial	Patients used either intrauterine insemination or timed intercourse to achieve fertilization, and the patients outcomes for each method of insemination could not be separated from the aggregate data. In addition, some patients had stage I endometriosis and male factor was involved in five cases.
Mendes et al. [130]	Randomised controlled trial	The pregnancy rate was only reported for one group of patients. Two of the authors were asked to supply a pregnancy rate for the other study arm but they failed to respond.

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Table 2: Summary of the final exclusion process based on the full text article (cont'd)

Study	Study Type	Reason for Exclusion
Suginami et al. [76]	Randomised controlled trial	The study included 20 normoprolactinaemic women (WHO group 1 and 2), and did not report results separately for the women with PCOS.
Yarali et al. [78]	Randomised controlled trial	Already analysed in a systematic review (van Wely et al. [116]) that was included in this report.
Bennick et al. [57]	Randomised controlled trial	The study included 172 women with CC-resistant normogonadotrophic chronic anovulation (WHO group 2), but the cause of anovulatory infertility was not outlined specifically and it is not clear how many of these women were diagnosed with PCOS (if any).
Boostanfar et al. [64]	Randomised controlled trial	The study included 86 anovulatory women, under 40, undergoing ovulation induction, but the cause of anovulatory infertility was not outlined specifically and it is not clear how many of these women were diagnosed with PCOS (if any).
Bayram et al. [131]	Randomised controlled trial	Only abstract published.
Ernest et al. [132]	Randomised controlled trial	The study included 20 CC-resistant WHO group II anovulatory subfertile women, undergoing ovulation induction, but the cause of anovulatory infertility was not outlined specifically and it is not clear how many of these women were diagnosed with PCOS (if any).
Shalev et al. [133]	Randomised controlled trial	The study included 250 women with unexplained infertility or with infertility caused by ovulation disturbances, undergoing ovulation induction; the cause of anovulatory infertility was not outlined specifically and it is not clear how many of these women were diagnosed with PCOS (if any).
Bider et al. [134]	Randomised controlled trial	The study included 74 normoandrogenic and anovulatory women who failed to respond to CC therapy or had an ovary of the PCOS type and were undergoing ovulation induction; the cause of anovulatory infertility was not outlined specifically and it is not clear how many of these women were diagnosed with PCOS (if any).
Nichols et al. [135]	Randomised controlled trial	The study included 115 premenopausal and anovulatory women undergoing ovulation induction; the cause of anovulatory infertility was not outlined specifically and it is not clear how many of these women were diagnosed with PCOS (if any).
De Vita [136]	Randomised controlled trial	Only abstract was published in English.

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Table 2: Summary of the final exclusion process based on the full text article (cont'd)

Study	Study Type	Reason for Exclusion
Lass et al. [137]	Analysis of 2 prospective randomised controlled trials	This is a retrospective analysis study; it included 465 WHO group II anovulatory women undergoing ovulation induction; the cause of anovulatory infertility was not outlined specifically and it is not clear how many of these women were diagnosed with PCOS.
van Weissenbruch et al. [138]	Randomised controlled trial	Pregnancy rates were not reported.
van Santbrink and Fauser [139]	Randomised controlled trial	The study included 37 normogonadotropic clomiphene-resistant oligo-and amenorrheic infertile women undergoing ovulation induction; the cause of anovulatory infertility was not outlined specifically and it is not clear how many of these women were diagnosed with PCOS (if any).
Nestler et al. [140]	Randomised controlled trial	Pregnancy rates were not reported in the published report of this study.
De Leo et al. [141]	Randomised controlled trial	This study crossed-over most patients of one treatment group to the other treatment group. The published report of this study provides unclear reporting of study results. The investigators pooled data on patients receiving two different treatment protocols and the data for each group couldn't be separated from the aggregated data; there are numerical discrepancies in the tables reporting on different outcomes of the two treatments.
Bider et al. [82]	Randomised controlled trial	The study included 42 cases with unexplained and anovulatory infertility; no subgroup of women with PCOS was identified; results are not reported separately.
Sturrock et al. [90]	Randomised controlled trial	The study recruited only 19 women and one of the study groups had ≤10 subjects. Not clear how the recruited women were crossed over between treatments and there were numerical discrepancies in the reported results.
Farquhar et al. [142]	Randomized controlled trial	Already analysed in a Cochrane Review (Farquhar et al. [114]) that was included in this report.
Vandermolen et al. [21]	Randomized controlled trial	Already analysed in a Cochrane Review (Lord et al. [115]) that was included in this report.

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Table 2: Summary of the final exclusion process based on the full text article (cont'd)

Study	Study Type	Reason for Exclusion
Kocak et al.[72]	Randomized controlled trial	Already analysed in a Cochrane Review (Lord et al. [115]) that was included in this report.
Yarali et al. [143]	Randomized controlled trial	Already analysed in a Cochrane Review (Lord et al. [115]) that was included in this report.
Balasch et al. [83]	Randomized controlled trial	Already analysed in a Systematic Review (van Wely et al. [116]) that was included in this report.
Pearce & Hamid [144]	Randomized controlled trial	The study included both ovulatory and anovulatory women with a history of three consecutive spontaneous first trimester miscarriages and PCOS.
Andoh et al. [145]	Randomised controlled trial	The study included 37 infertile women with PCOS resistant to CC, undergoing ovulation induction with 3 regimens of HMG (fixed dose, low- dose step-up and step-down). Although this study had a parallel design, it was not clear how patients were allocated in the end; results were not clearly reported (some women had more than one regimen and the reporting was confusing).
Prelevic et al. [146]	Randomised controlled trial	The study included 28 infertile women with PCO resistant to CC, undergoing ovulation with HMG and an adjuvant (octreotide) or HMG alone. The study design was a combination of parallel and crossover and in one group women acted as their own controls. Data were not clearly reported and there were discrepancies in the data reported in various tables.
Branigan and Estes [147]	Randomized controlled trila	The study population included 48 CC-resistant women suffering from chronic anovulation. However, it is not clear whether the chronic anovulation is associated with PCOS.
Wang and Soong (1996) [148]	Prospective controlled trial	Not a randomized controlled study.
Homburg et al (1995) [149]	Non-randomised comparative prospective study	Not a randomized controlled study.

APPENDIX D: OI DRUGS USED FOR ANOVULATORY INFERTILITY

The most frequently used OI drugs for managing anovulatory infertility include clomiphene citrate (CC) therapy as well as several different types of gonadotrophin therapy for those who do not respond to CC therapy (do not ovulate or do not conceive despite ovulation). Recently, insulin sensitizers have been proposed for inducing ovulation and achieving pregnancy in women with anovulatory infertility associated with PCOS.

The following commentary summarizes the information published in the background material included for this review (articles reporting clinical reviews, commentaries, and discussions on the topic) referring to these agents' mechanism of action, administration, risks, benefits, adjunct therapy, and costs.

1. CC Therapy

CC, is a non-steroidal estrogen receptor antagonist agent, which is generally offered as the first line treatment for induction of ovulation in women with adequate levels of estrogen and normal levels of FSH and prolactin [3,8,10,11,13,15,18,23,24,25,26,29,31,50,55,58,74,130]. These patients include those with inappropriate gonadotrophin release (with an increased ratio of LH to FSH), as it occurs in women with PCOS.

Although CC has been in widespread clinical use for the last 40 years, its mechanism of action is still unclear [3, 11, 15, 16, 18, 19, 23, 24, 25, 26, 29, 49, 50, 55, 58, 65, 69, 74]. It is thought to have a mixture of effects on the hypothalalmus, pituitary and ovaries. CC administration is thought to induce ovulation by binding to estrogen receptors in the hypothalamus and pituitary and causing an increase in the gonadotrophin releasing hormone (GnRH) pulse frequency and a subsequent elevation in endogenous gonadotrophin secretion. Other mechanisms of action may also be operative [3].

Current commercially available preparations include Clomid®, Serophene® and generic equivalents [8, 17, 23, 26, 58]. Treatment protocols can vary but generally CC is prescribed for a 5-day period starting the day 2 to day 6 after spontaneous or induced menstrual bleeding [3, 8, 11, 15, 21, 22, 23, 24, 25, 26, 31, 33, 39, 40, 49, 50, 52, 53, 55, 58]. It is administered orally (50mg tablets) once a day and the initial dose is 50 mg.

The manufacturers of CC recommend doses of up to 100mg/day for 5 days and only for a total of 3 cycles [49,50]. In clinical practice doses greater than 100mg/day (150-250/day) or prolonged regimens have been used in some CC resistant women, especially those with increased BMI [3, 8, 11, 21, 22, 23, 24, 31, 33, 39, 40, 49, 50, 52, 53, 55, 58, 86].

According to the literature reviewed [3, 11, 15, 18, 21, 22, 24, 26, 33, 39, 49, 50, 53, 55, 73]:

- Every patient has a threshold dose of CC and going beyond it does more harm than good as its use may produce serious complications and adverse effects (anti-estrogenic and anti-fertility effects on the cervical mucucs and endometrium).
- Most CC-induced pregnancies occur within the first 6 ovulatory cycles, once the threshold dose is achieved (usually at doses no greater than 100mg/day for 5 days). Doses higher than 150mg/day for 5 days and treatment periods longer than 6 months are not usually effective in terms of induced-pregnancy.
- In general, when CC fails to induce ovulation or conception after treatment for ≤ 6 months (or ≤ 6 cycles), the situation is considered CC resistance or failure and more diagnostic investigations and alternative treatments are usually called for.

The ovulatory response can be assessed by ultrasound scan, endometrial biopsy, blood and urine tests [3, 11, 17, 18, 23, 24, 29, 33, 49, 50, 53, 55, 58, 73, 123]. CC-induced pregnancy can be defined by positive urine or serum beta-HCG test [29].

Potential side effects of CC therapy include: cramping, ovarian enlargement, hot flashes, nausea, vomiting, breast tenderness, mood changes, depression, headache, insomnia, intermenstrual spotting and menorrhagia, gastro-intestinal distress, and blurred vision or visual symptoms such as flashes or spots [22, 23, 24, 26, 49, 50, 53, 55, 69, 150, 151]. Less common visual symptoms may occur, warranting discontinuation of therapy [24, 49]. A common problem presenting immediately following an unsuccessful treatment cycle with CC is functional ovarian cysts [49, 50, 152].

Complications associated with CC therapy relate primarily to the risk of multiple gestations with reported rates ranging from 5% to 12.3% [3, 8, 9, 11, 15, 24, 26, 31, 33, 49, 50, 55, 69]. Twin and triplet gestations occur in up to 10% and 0.5%, respectively, of CC-induced pregnancies [3, 9, 13, 14, 24, 26, 31, 69]. The overall incidence of higher order gestations (triplets or higher order) is around 1% [13, 14, 49].

The risk of developing OHSS for women treated with CC is estimated at less than 1% [3, 49]. Miscarriage rates of up to 30% have been reported (Cumming, personal communication).

Published estimates suggest that the rate of pregnancy-related complications or incidence of birth defects are not increased in CC-treated women when compared to those reported for spontaneous conceptions [3, 9, 11, 15, 24, 26, 49, 53, 55, 58, 151]. Some concerns have been raised about the teratogenic effects CC may have on the developing fetus [65]. There may be an increased chance of bilateral tubal pregnancy and coexisting tubal and intra-uterine pregnancy when conception occurs in relation with CC therapy [151].

An association between the prolonged use of CC and an increased risk of developing ovarian cancer have been reported, mostly in women with unexplained infertility [5, 15, 26, 28, 49, 50, 55, 124, 153, 154, 155] (http://www.asrm.org). Although the initial studies did not quantify the risk and no interpretable data are currently available on this potential relationship, it has been recommended that in most cases CC should not be continued beyond 6 ovulatory cycles [15, 16, 18, 33, 39, 49, 50, 53, 55, 124, 152].

Contraindications for the use of CC therapy include liver disease or history of liver dysfunction, uncontrolled thyroid or adrenal dysfunction, presence of ovarian cysts or ovarian cyst enlargement, substantial or residual ovarian enlargement, and presence of pregnancy [3, 18, 24, 26, 49, 55, 73, 152]. As the presence of other medical problems may affect the use of CC, its use is contraindicated in patients who have depression, organic intracranial lesions, inflamed veins due to blood clots, or abnormal uterine bleeding [18, 55, 73, 152].

2. Gonodotrophin Therapy

Gonadotrophin therapy using injectable preparations has been indicated and used to manage anovulatory infertility in women who failed to ovulate or become pregnant despite ovulation after CC therapy [5, 16, 24, 25, 31, 39, 48, 49, 55, 58, 59, 67, 68, 70, 77]. Injectable gonadotrophins are medical preparations of FSH and LH, usually used in anovulatory infertility to bypass a body's non-functional hypothalamic-pituitary-ovary axis.

The success of this therapy is associated with the women's type of anovulatory infertility and age [5, 16, 24, 25, 31, 39, 48, 49, 55, 58, 59, 67, 68, 70, 77]. Women with low levels of estrogen and gonadotrophin have better results than those with normal levels of estrogen and gonadotrophin (including those with PCOS).

Gonadotrophin medication supplied in mutlidose vials is administered by intramuscular (i.m.) or subcutaneous (s.c.) injection daily or on alternate days for 7-14 days or longer [15, 18, 23, 24, 28, 32, 39, 48, 49, 53, 55, 82] (Cumming, personal communication). Treatment is usually started a few days after a spontaneous or induced menstrual bleeding with duration. The dose given may vary from patient to patient and is usually tailored according to the woman's age, weight, serum concentration of follicular phase FSH, the presence/absence of polycystic ovaries and any evidence of ovarian response to previous stimulation [81]. Protocols are adjusted up and down according to individual response.

The suggested initial dose is 75-150 IU/day in most patients. Further increases may be required if there is no response [15, 18, 23, 24, 28, 32, 39, 48, 49, 53, 55, 56, 61, 82]. It appears that women with increased BMI require higher doses of gonadotrophins than lean women [39, 52].

Human chorionic gonadotrophin (hCG), made from pregnancy urine and placental tissue, is administered in a single i.m. injection (of 5,000 or 10,000 IU) during gonadotrophic therapy in most cases both to trigger ovulation and for lutheal support [11, 15, 18, 23, 28, 39, 48, 53, 55, 60, 81, 86, 122]. Both dosage and timing of hCG administration vary according to the protocol being used. Commercial names for hCG include Profasi®, Pregnyl®, Novarel® and Ovidrel®.

The use of gonadotrophins is associated with an increased risk of developing miscarriages and multifollicular developments (which may lead to complications such as OHSS and multiple gestations) [15, 18, 50, 53, 55, 68, 69, 80]. For yet unclear reasons the miscarriage rate may be higher (≤30%) in gonadotrophin-stimulated cycles than in the unstimulated cycles.

Mild to moderate OHSS, with marked ovarian enlargement and lower abdominal pain, occurs in 3-7% of the cycles [9, 13, 15, 23, 28, 60, 81, 123]. The incidence of severe OHSS (which is potentially life threatening and requires close monitoring and hospitalization in most cases) ranges between <0.01% to 3.9% and is higher for women with estrogenic anovulation [9, 13, 15, 28, 50, 55, 58, 60, 81].

The risk of multiple gestations associated with the use of gonadotrophin therapy was estimated between 10% and 30% [8, 15, 28, 55, 58, 61, 68]. Although the majority of these were twin gestations, they include a significant number of triplets or higher order gestations (about one-third) [13, 15, 61], (http://www.asrm.org).

Recently published evidence raised concern about a possible association between the use of gonadotrophins and the risk of ovarian cancer [9, 15, 28, 55, 61, 124]. Although to date no convincing data exist regarding such relationship [157-159], (http://www.asrm.org), it is recommended to limit the duration of the gonadotrophin therapy.

With gonadotropin therapy the rate of ectopic or tubal pregnancies is slightly increased from 0.01% to 2% (in the general population) to 1% to 3 % [28] (http://www.asrm.org). Heterotopic pregnancies (combined ectopic and intrauterine pregnancies) occasionally occur with HMG. The incidence of heterotopic pregnancies in women stimulated with gonadotrophin therapy is approximately 1% compared to 0.01% to 0.025 in the unstimulated population [28].

According to the American Society for Reproductive Medicine, the rate of birth defects after gonadotropin therapy is no higher than in the general population, and children conceived through this therapy are developmentally no different than their peers (http://www.asrm.org).

Careful investigations (using ultrasonography and other screening tests) before starting therapy are recommended to rule out other factors and to detect polycystic ovaries [3, 11, 15, 18, 23, 28, 32, 39, 48, 49, 53, 55, 56, 58, 60, 61, 81, 82, 123]. Close monitoring of the follicular development during each cycle with ultrasound scans and serum estradiol measurement is required to determine the number and size of follicles and the corresponding estradiol levels and to avoid complications associated with multiple follicular development.

Careful hormonal and ultrasonographic monitoring is also required to determine when to administer hCG (intended as a substitute for the endogenous LH surge) [11, 15, 18, 23, 28, 39, 48, 53, 55, 58, 60, 81, 86, 122]. In some cases there is no need for exogenous hCG as spontaneous LH surge occurs. In overstimulated cycles, it has been recommended to withhold hCG, in order to avoid complications associated with multiple follicular development.

Induction of ovulation with exogenous gonadotrophins is relatively contraindicated in the presence of an untreated intracranial lesion or in the presence of ovarian tumors or enlargements not due to PCOS [28].

Different gonadotrophin preparations

Most frequently used gonadotrophin preparations, known as human menopausal gonadotrophin (HMG) preparations, are derived from human urinary sources [3, 11, 15, 19, 23, 32, 39, 48, 49, 53, 55, 79, 80, 85, 123]. These preparations (Repronex®, Pergonal®, Humegon®) provide both FSH and LH. Drawbacks of using HMG preparations include the negative effects of large quantities of potentially allergenic urinary proteins (non-gonadotrophin protein constitute >95% of total protein content).

Side effects of HMG therapy include fluid retention, weight gain, fever, nausea and vomiting mood swings and ovarian enlargement (which occurs in approximately 20% of cases and may result in OHSS) [8, 23, 58]. Thromboembolic events are possible complications of this therapy [58, 60].

Ovulation and pregnancy rates after HMG in women treated for anovulatory infertility associated with PCOS may be affected by hypersecretion of androgen and high LH levels in many cases, which are thought to be significant causes of reduced pregnancy rate and miscarriage [39, 48, 49, 53, 55, 79, 80, 86, 129]. For these reasons and because of the increased risk of multiple follicular developments in these women they have been and continue to be a special target for the new developments in commercial gonadotrophin preparations.

The newer gonadotrophin preparations (urofollitropin and follitropins alpha and beta) are highly purified preparations (non-gonadotropin protein accounts for < 5% of the total protein content) [11, 15, 19, 23, 32, 39, 49, 53, 78, 80, 85]. Urofollitropin (Fertinex® or Metrodin MP® or Neo-Fertinom®) is a pure urine-derived preparation, nearly all FSH (<0.1 IU of LH contamination). Follitropins alpha and beta (Gonal-F® and Follistim®) are recombinant FSH synthetic preparations, derived from recombinant DNA technology. All these new preparations can be given by s.c. injection, an advantage over the i.m. route used in the past for the older urine-derived HMG preparations.

The biochemical and pharmacokinetic characteristics of recombinant forms of pure FSH (rFSH) are very similar to those of the urinary forms of pure FSH (uFSH) [19, 80]. Using rFSH appears to have two main advantages: relatively easy to obtain and the total absence of LH activity [3, 19, 23, 69, 80]. Other advantages evolving from the above mentioned ones are independence of urine collection, absolute source control and batch to batch consistency [19, 69, 80]. Also, it appears that rFSH preparations have greater bioactivity and thereby require a lower dose and shorter duration of administration [11, 48, 79, 80].

Other strategies

Alternative strategies have been developed with the aim to improve the outcome in terms of achieving successful pregnancy and reducing the risk for OHSS, multiple gestation, and miscarriages. Several low-dose regimens of various gonadotrophin preparartions have been designed and used (such as low-dose step-up, step-down and sequential step-up and step-down protocols) [3, 5, 11, 18, 30, 32, 48, 49, 53, 68, 69, 78, 79, 80, 123, 129]. These regimens use lower doses of gonadotrophins for longer intervals in order to create monofollicular development and ovulation. All require careful monitoring by US and other means.

Beyond the use of low-dose regimens, other strategies used with the same pursposes, include the use of pulsatile gonadotrophin releasing hormone (GnRH) therapy and the use of pre-stimulation protocols (combined oral contraceptive pills or a GnRH analog therapy).

The administration of GnRH therapy is primarily indicated for patients with low levels of estrogen and gonadotrophins (WHO group 1) and normal pituitary function [3, 15, 16, 39, 41, 50, 53, 55, 83, 84]. Treatment with GnRH has been extended to infertile cases belonging to WHO group 2 and PCOS based on the rationale that the exogenous GnRH pulses could override the abnormal pattern of endogenous GnRH secretion and induce ovulation and successful pregnancy [31, 39, 41, 53, 55, 83, 84, 113]. Synthetic GnRH is available as gonadorelin hydrochloride (Factrel®) or gonadorelin acetate (Lutrepulse®).

OHSS occurs in <1% of cases treated with pulsatile GnRH therapy and the incidence of multiple gestations is 8.3% [15, 55]. However, reported pregnancy rates are low and abortion rates are high [15, 39, 41, 55]. Miscarriage rates have been reported as high as 45% [53].

No interpretable data are available on the potential impact of the use of pulsatile GnRH therapy on the incidence of ovarian cancers [55]. The necessity of closely monitoring each cycle of GnRH therapy appears to be the same as with using gonadotrophin therapy [15].

Some protocols have used GnRH analog therapy (GnRHa) before gonadotrophin therapy to trigger ovulation in infertile patients with PCOS [19, 23, 25, 31, 39, 41, 53, 54, 59, 69, 83, 84, 85, 86, 87]. The idea behind pre-treatment with GnRHa (such as Lupron®) was to suppress high LH levels and, by curbing the release of endogenous LH, to improve the rate of monofollicular development and reduce the miscarriage rate.

Pre-treatment with GnRHa (using agonist or antagonist preparations), does not seem to prevent OHSS and/or affect pregnancy rates [19, 23, 25, 31, 39, 41, 53, 54, 59, 69, 83, 84, 85, 86, 87].

However, it has been suggested that the prevention of premature luteinization by GnRHa may improve pregnancy outcome by decreasing the high spontaneous abortion rate in these women [31].

The use of GnRHa is associated with symptoms of estrogen deprivation such as hot flushes, mood swings, nausea, body aches, vaginal dryness, fatigue, irritation, headache, breast tenderness and abnormal uterine bleeding [23, 83]. There is evidence to suggest a significant loss of cortical bone at the level of the lumbar spine in women treated with GnRHa [83].

3. Insulin-sensitizing agents

On the theory that insulin resistance and hyperinsulinemia impede ovulation and may be important contributors to the pathophysiology of PCOS, it has been postulated that insulin- sensitizing (lowering) agents might improve the abnormal endocrine milieu associated with PCOS, resulting in an increase in ovulatory cycles and pregnancy [12, 21, 25, 34, 45, 47, 49].

Insulin sensitizers that have been evaluated in clinical trials for their ability to induce ovulation in women with hyperandrogenism and insulin resistance include metformin, troglitazone, and rosiglitazone [5, 25, 32, 34, 42, 43, 49, 92, 93, 94, 115]. Other agents, which mediate the action of insulin, have been recently introduced in the market and are currently being studied [93, 115].

Metformin hydrochloride (with brand names including Glycon®, Glucophage XR®, and Glucophage®) [99, 104] is a member of the biguanide class of oral antidiabetic agents, which has been more widely investigated than other insulin sensitizers for this indication [12, 24, 25, 32, 34, 44, 45, 49, 51, 91, 92], Its mechanism of action is still poorly understood but it is known to work primarily by suppressing hepatic glucose production [37, 42, 43, 94] and to enhance the peripheral action of insulin without insulin secretion [25, 42, 43, 44]. In women with PCOS its use results in reduction of ovarian androgen production, attenuation of insulin levels and appears to enhance both spontaneous and CC-induced ovulation.

The starting dose is 500 mg daily [33]. If the woman's cycle remains irregular, this dose may be increased to 500 mg twice daily for a minimum of 3 months, to 500 mg 3 times daily or 850 mg twice daily. If menses are going to return on metformin alone this usually occurs in 2-4 months and addition of CC is recommended as appropriate for those without return of menses in that time [24, 32].

The therapeutic range of 1,500 to 2,500 mg/day of metformin in 2 to 3 divided doses is usually required to see an effect [24, 25, 32, 33, 34, 42, 43, 44, 50, 91]. The majority of studies published on the use of metformin for OI in women with PCOS administered 500mg tablets 3 times daily with meals [34, 50]. The manufacturers of metformin suggest 2,500 mg daily as the maximum dose.

Serum progesterone measurements are performed or the patient can keep a BBT chart to indicate whether ovulation occurs [33, 24].

The use of metformin is associated with gastrointestinal side effects such as nausea, vomiting, and abdominal bloating but no serious adverse effects have been reported [24, 33, 34, 37, 42, 43, 44, 49, 91, 93, 115]. Nausea, diarrhea, and abdominal bloating may be minimized by a gradual increase in dose and are almost always transient [24, 33, 34, 43].

Concern has been raised in relation to potential teratogenic effects of metformin [33,37,44,49]. Although its use seems to be safe during pregnancy, it is recommended to stop its use as soon as pregnancy is diagnosed [24, 33, 49]. However, the lack of evidence of teratogenic effect and the possibly beneficial effect on the wellbeing of the pregnancy has led a number of specialists to recommend that the drug should be continued certainly through the first trimester of pregnancy (Cumming, personal communication). Some data suggest that metformin can reduce the risk of miscarriage in women with PCO and there is evidence that the risk of gestational diabetes is also reduced in these women (Cumming, personal communication).

In rare cases it has caused fatal lactic acidosis [24, 34, 42, 43, 91]. Therefore, it has been suggested that its use is contraindicated for patients with a predisposition to elevated lactate levels (such as those with renal, hepatic, or major cardiovascular disease or hypoxia) [24, 43, 91, 93].

Other insulin sensitizing agents include the thiazolidinedione group of antidiabetic drugs, of which the most widely researched in the context of PCOS is troglitazone (Rezulin®) [21, 25, 32, 34, 40, 43, 51, 93, 115]. However, because of safety concerns related to liver toxity and other adverse effects this agent was withdrawn from the market in March 2000.

Rosiglitazone maleate (Avandia®) is another member of the thiazolidinediones that has been recently proposed and researched in women with CC-resistant PCOS [94, 115] (http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a699023.html). It can be taken orally (tablets equivalent to 2mg, 4mg, and 8 mg, usually once or twice daily) and works by reducing the body's resistance to the action of insulin without stimulating insulin secretion. Dosage is different for different patients and is based on the medical condition and response to therapy.

It is approved by FDA for use in the management of type 2 diabetes in adults (http://www.fda.gov/cder/consumerinfo/druginfo/avandia.htm), (http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a699023.html). It is not indicated for type 1 diabetes or diabetic ketoacidosis.

Possible side effects include: upper respiratory tract infections ,headaches, muscle aches, tooth aches, sore throat, inflammation of the sinuses, back pain, weight gain, tiredness, diarrhea, [94], (http://www.fda.gov/ cder/ consumerinfo/ druginfo/ avandia.htm), (http://www.nlm.nih.gov/medlineplus/ druginfo/ medmaster/ a699023.html). It may cause a slight decrease in red and white blood cells. Like other thiazolidinediones, rosiglitazone can cause fluid retention, alone or in combination with other antidiabetic agents, which may exacerbate or lead to heart failure.

It is not recommended in patients with kidney or liver disease, enlarged heart, swelling, pregnancy (http://www.fda.gov/cder/consumerinfo/druginfo/avandia.htm), (http://www.formularyjournal.com/formulary/article/articleDetail.jsp?id=55275) [118, 156].

Although rosiglitazone is in the same class of antidiabetic drugs as troglitazone, it is metabolized by different liver enzymes and it appears to pose less risk of hepatotoxicity (http://www.formularyjournal.com/formulary/article/articleDetail.jsp?id=55275), (http://www.fda.gov/cder/consumerinfo/druginfo/avandia.htm), [94, 115, 118, 156,]. Currently, the FDA is monitoring the occurrence of adverse events arising from the use of rosiglitazone, and is confident that it has the same benefits as troglitazone but not the same risk. However, regular monitoring of liver enzyme levels is recommended.

No evidence of teratogenecity has been reported in either pre-clinical or clinical trials of rosiglitazone.

APPENDIX E: INFORMATION EXTRACTED FROM PRIMARY AND SECONDARY RESEARCH STUDIES

Table 3: Primary quantitative research studies

Study (authors, publication date, design, setting)	Study population	OI drug therapy	Reported results of interest· and Author(s)' conclusion	Reported complications and adverse events
Timmerman-van Kessel et al.,[107] 2000 **Design:** Subgroup analysis within a multicenter RCT to compare endocrine changes in follicular phase in patients with PCOS treated with either pulsatile IV GnRH after GnRHa (agonist) down-regulation or with CC. **Setting:** Infertility clinic (in the Netherlands)	N=30 healthy women (age < 40 ys, primary infertility, normal semen analysis) with PCOS (amenorrhea or oligomenorrhea, LH>6.5 IU/L, LH-FSH ratio>1.5) **GnRH group:** n=16 (age of 22-31 ys, infertility duration of 1-2.75 y) **CC group**: n=14 (age of 21-31y, infertility duration of 1-2.6 ys) NSS differences in terms of mean values of age and infertility duration and endocrine characteristics serum LH, FSH, and serum E_2)	After *central randomization*, patients assigned to **GnRH group:** daily GnRHa (nafarelin) intranasally (400micro grams, Synarel; Searle, Maarsen, The Netherlands) for 3 wk and started pulsatile IV GnRH, gonadorelin, (10 micrograms/90 min; HRF; AHP-Pharma BV, Hoofddorp, The Netherlands). **CC group**: CC (50 mg; Clomid, Yamanouchi Pharma, Leiderdorp, The Netherlands) on cycle days 3-7 or after an episode of withdrawal bleeding. If necessary, withdrawal bleeding induced by P (100 mg i.m., Progestine, Organon, BV, Oss, The Netherlands) Monitoring of treatment response by ovarian US and serum concentrations of E_2, LH and FSH. Same protocols used until pregnancy occurred and were stopped after a max. of 3 treatment cycles **Note:** 2 women from the CC group did not receive treatment because they dropped out of the study.	**Ovulation:** ·Ovulation occurred in 47% (19/40) of all initiated cycles in GnRH group and in 60% (15/25) in CC group. ·In CC group, ovulation rate per patient was 66%. **Pregnancy:** ·Pregnancy rates per initiated cycle were NSS between groups (10% in GnRH group vs. 16% in CC group). ·Pregnancy rate per patient was 33% in CC group and 25% in GnRH group. **Conclusion:** "No significant endocrine differences were observed between GnRH and CC treatment. However, there was a significant increase in the serum LH concentration during the follicular phase in the GnRH group. Increments of LH in the GnRH group may be due to recovery of endogenous LH secretion." "Presumed clinical benefits, due to endocrine differences of GnRH (preceded by GnRHa down-regulation) as compared with CC could not be demonstrated in our study protocol, possibly because of small numbers of patients"	**Note:** no statements on incidence of miscarriages, multiple pregnancies and/or OHSS observed in the women included

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Table 3: Primary quantitative research studies (cont'd)

Study (authors, publication date, design, setting)	Study population	OI drug therapy	Reported results of interest* and Author(s)' conclusion	Reported complications and adverse events
Hassan et al., [108] 2001 **Design:** Prospective randomized controlled trial conducted to study the effect of ketoconazole on CC responsiveness in infertile women with PCOS **Setting:** IVF-ICSI Centre (in Egypt)	N=97 infertile women with PCOS and insulin resistance (undergoing OI over 20 mo duration; male partner's normal semen analysis) **GroupA:** n=37 **Group B**: n=43 Before treatment the mean value of serum testosterone and insulin were not different between the groups.	All women were randomly divided (*random-number table*) into: **Group A** received OI with CC for 3-6 cycles; had 136 cycles over 9 mo; initially, 48 women recruited for study; 11 women dropped out after 1-3 cycles and were excluded from study. **Group B** received pre-treatment with ketoconazole (400 mg/day) for 85 days before OI with CC (100-150 mg daily); had 180 OI cycles over 9 mo; initially, 49 women were recruited for study; 6 women dropped out and were excluded from study. In both groups, only patients who persistently failed to respond to CC therapy (*not clear whether failed to ovulate only or failed to conceive or failed to ovulate or conceive)* with 150 mg/day were shifted to HMG. Initial assessment included BMI, waist-to-hip ratio, Ferriman-Gallway score, Acanthosis nigricans, serum total testosterone level, insulin response to 75 g oral glucose load (Insulin curve), as well as serum FSH, LH and prolactin. Follow up for group B included also pattern of menstrual cycle, weight, serum transaminases, ovulation scanning, serum progesterone, testosterone and insulin levels, as well as any side effects noticed by patient.	*Incidence of CC resistance was SS less in Group B than in Group A (11.6% vs. 32.4; p<0.05) **Ovulation** *In CC-responsive women, those from Group B showed SS higher incidence of monofollicular response (38%) and lower incidence of triple follicular response (13%) vs. those in Group A (23% and 27%, respectively) (p<0.05). **Pregnancy** *In Group A, clinical pregnancy rate per patient was 21.6 % (8/37) and incidence of cardiac pulsation per patient was 13.5% (5/37). *In Group B, pregnancy rate per patient was 39.5% (17/43) and cardiac pulsation per patient was 37.2% (16/43). **Conclusion** "Ketoconazole improved clomiphene responsiveness in PCOS patients and attenuated its untoward biological effects." "Because of its clinical implications, clomiphene resistance in PCOS women possibly needs to be redefined".	**Miscarriages/Abortions:** *In Group A, rate of abortion after cord pulse was 20% (1/5) (which occurred among twin pregnancies in this group). *In Group B there were no abortions after cord pulse. **Multiple pregnancies:** *In Group A there were 5 sets of twins and 1 set of triplets. *In Group B there were 5 sets of twins and 3 sets of triplets. **Note:** no statement on absence/presence of OHSS observed in the women included

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Table 3: Primary quantitative research studies (cont'd)

Study (authors, publication date, design, setting)	Study population	OI drug therapy	Reported results of interest* and Author(s)' conclusion	Reported complications and adverse events
Parsanezhad et al.,[109] 2002 **Design:** Prospective, double blind RCT, placebo-controlled conducted to evaluate the effects of using bromocriptine combined with CC in CC-resistant women with PCOS and normal PRL level **Setting:** Referral university hospital	N= 100 infertile women with PCOS (chronic anovulation; typical US appearance of PCOs -multiple small cysts scattered around periphery and highly echiogenic stroma) and CC-resistance (ovulation and normal luteal phase not achieved with highest dose of CC for 5 days for at least 5 cycles) HSG, post-coital test and semen analysis normal in all women. All women failed to ovulate with 200mg of CC for 5 days, combined with 10,000 IU of hCG. **Treatment group:** mean age of 25.02±2.7y; mean infertility duration of 4.53±3.1y; mean BMI of 30.33±4.11 Kg/m^2 **Control group:** mean age of 24.87±2.9y; mean infertility duration of 4.02±1.9 y; mean BMI of 29.82±4.35 Kg/m^2	Hormonal assessment completed before inclusion, on cycle days 3-5 and 20-22 of spontaneous/progesterone-induced cycle and repeated after 3 and 56 mo of therapy with CC plus bromcriptine or CC plus placebo given *in odd-even number double blind format.* Subjects were given 150mg of CC from cycle days 5 to 5 (after spontaneous/induced cycle) and bromocriptine (or placebo) in a dose of 2.5 mg, 3 times/day (after gradually building up dose). Bromocriptine or placebo given continually, without interruption between cycles. Folliculometry done on cycle day 16 or 17 (7 days after last dose of CC) same day when hCG (10,000 IU) was injected. If menstruation started after 2 wk of hCG, next cycle started and continued for a max. of 6 cycle. If menstruation delayed and a negative hCG observed, beta-hCG assay was repeated after 10 days and 100 mg of progesterone injected i.m.	**Ovulation:** *NSS difference in ovulation rates between groups *In treatmernt group, 18.3% ovulated and in the control group 14.9% of women ovulated **Pregnancy:** *NSS difference between groups in terms of pregnancy rate *During 6 mo, 7 women in treatment group and 8 women in control group became pregnant **Conclusion:** "The only significant effect of long-term bromocriptine therapy in CC-resistant women with PCOS was to lower the serum PRL concentration. It is also concluded that 10%-15% of patients with PCOS experienced occasional ovulatory cycles and pregnancy whether or not they were on treatment."	**Note:** no statement on presence/absence of miscarriages/abortions, multiple pregnancies or OHSS observed in the women included **Side effects:** Patients in the treatment group experienced dizziness (63.8%), nausea (51.1%), fatigue (12.8%), vomiting (19.1%), confusion (8.5%), headache (10.6%), fainting (6.4%), and insomnia (6.4%).

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Table 3: Primary quantitative research studies (cont'd)

Study (authors, publication date, design, setting)	Study population	OI drug therapy	Reported results of interest* and Author(s)' conclusion	Reported complications and adverse events
Hugues et al., [110] 1996 **Design:** Prospective RCT conducted to compare safety and effectiveness of 2 low-dose FSH regimens in PCOS **Setting:** not clearly stated (in France)	N=56 women with anovulatory infertility (WHO group 2) associated with PCOS (chronic anovulation; typical US findings of >10 follicles <9mm in diameter in each ovary, a hyperechogenic central stroma, and ovarian area >8 cm^3; high serum LH:FSH ratio, and serum androgens). *All failed to ovulate or become pregnant with CC. *Normal male partner sperm parameters and hystero-salpingogram were pre-requisites for admission. All women were randomly allocated to **Step-up group:** n=29 (mean age of 28.6±0.6 y; mean BMI of 24.7±0.7 Kg/m^2; mean infertility duration of 3.3±0.4 y) **Sequential group:** n=27 (mean age of 28.7±08 y; mean BMI of 24.9±0.1 Kg/m^2; mean infertility duration of 3.6±0.5 y) NSS difference in the clinical and endocrine features between groups.	Patients randomly allocated (*method of randomization not stated*) to receive: **Low dose step-up protocol:** 38 cycles started (from day 3 of menstruation) with 75 IU ampoule of u-FSH (Metrodin; Serono, France) increased by half an ampoule every 6 days until leading follicle reached 10mm in diameter (threshold), maintained until criteria for triggering ovulation (at least 1follicle of 18mm diameter), when 5000 IU of hCG (Gonadotrophin Endo; Organon, France) given to induce ovulation. No further hCG added to support luteal phase. Injection of hCG withheld if >3 follicles of >15 mm diameter were present. **Sequential low-dose step-up and step-down protocol:** For 34 cycles, FSH threshold dose reduced by half when leading follicle reached 14 mm in diameter until time for hCG administration (same as above). Ovarian response monitored by US exam of ovaries and measurement of serum oestradiol. Progesterone and LH concentrations and follicular growth rate evaluated during the cycle. **Note:** treatment cycles initiated in 56 women; 4 did not complete study (3 were in step-up group and 1 in sequential group) 3 because of ovarian hyperstimulation and 1 because of vaginal bleeding; their results not included in the statistical analysis	*Mean FSH threshold dose and time for follicular selection were similar in both groups. *SSdifference between groups (in favor of sequential protocol) in mean number of large (14-15mm) follicles ($p=0.05$) and mean estradiol levels ($p<0.05$) at time of hCG administration **Pregnancy:** in all, 35 pregnancies; NSS difference between groups * 20 pregnancies in step-up group * 15 pregnancies in sequential group * 12 ongoing pregnancies in each group (after miscarriages); * ongoing pregnancy per cycle was ~35% in both groups **Conclusion:** "A sequential step-up and step-down protocol seems to be a safe and effective regimen for ovulation induction in PCOS patients. Decreasing the FSH dose following step-up follicular selection may be an alternative method to avoid multifollicular development."	**Miscarriages/Abortions:** *Eight miscarriages observed in step-up group (40%) and 3 (15%) in sequential group **OHSS** *No severe (clinical) OHSS observed in any group **Note:** no statement on multiple pregnancy observed in the women included

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Table 3: Primary quantitative research studies (cont'd)

Study (authors, publication date, design, setting)	Study population	OI drug therapy	Reported results of interest* and Author(s)' conclusion	Reported complications and adverse events
Lidor et al., [75] 2000 **Design:** Prospective RCT conducted to evaluate efficacy of GnRHa (agonist) in preventing premature luteinization in patients with PCOS who had previous CC treatment **Setting:** Tertiary Medical Centre (in Israel) **Note:** primary and secondary infertility not defined	N=22 infertile women (mean age 31.1±5.7 y, mean infertility duration 2.5±1.0y; 17 had primary infertility, 5 had secondary infertility) with PCOS demonstrating premature luteinization (progesterone concentrations >1.5 ng/mL before administration of hCG) during ≥ 2 consecutive CC cycles **Group A:** n=10 **Group B:** n=12	All women randomly assigned (*method of randomization not stated)* to: **Group A:** after pregnancy excluded by serum hCG assay, cycles stimulated by i.m. FSH (Metrodin, Teva, Petach-Tikva, Israel) alone regardless of interval from last vaginal bleeding; individually adjusted regimen, employing a step-up of FSH (1 ampoule) every 4-5 days. **Group B:** pre-treatment with GnRHa (agonist) and then FSH; subcutaneous GnRHa (Decapeptil, Ferring, Kile, Germany; 0.1 mg injected daily) initiated after exclusion of pregnancy and continued until injection with hCG (10,000 IU; Chorigon, Teva, Petach-Tikva, Israel); 4-5 days after initiation of GnRHa, FSH added (same protocol as in Group A). The hCG administered when a dominant follicle achieved at least 16 mm in diameter and serum estradiol reached ≥ 400pg/mL. Each women undertook one cycle of treatment. Follicular development monitored by serum estradiol assays and vaginal US scans.	*Treatment duration and number of FSH ampules used did not differ between groups. *Incidence of premature luteinization differed SS between groups: 80% (8/10) in group A and 16.6% (2/12) in group B (p=0.03) **Pregnancy:** *In group A there were no pregnancies (0/10=0%) and in Group B there were 4 singleton pregnancies (4/12=33%) **Conclusion:** "Pituitary desensitization with GnRH analog in combination with FSH is superior to FSH-only treatment in PCOS patients who demonstrate premature luteinization during CC treatment." "These results further suggest that premature luteinization as seen in the FSH only treatment group dictates a low ovarian response and therefore a diminished pregnancy rate. In fact, once premature luteinization is avoided by the use of GnRHa as was done in group B, a significant improvement in fecundity is noted."	**Multiple pregnancies:** *No multiple pregnancies were detected in any group **OHSS:** *OHSS was not detected in any group. **Note:** no statement on miscarriage/abortion observed in the women included

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Table 3: Primary quantitative research studies (cont'd)

Study (authors, publication date, design, setting)	Study population	OI drug therapy	Reported results of interest* and Author(s)' conclusion	Reported complications and adverse events
Ergur et al.,[86] 1998 Prospective comparative and pilot study conducted to determine efficiency and comparison of 2 protocols, HMG plus GnRHa (analog) and low-dose HMG used to reduce multifollicular development in CC-resistant patients with PCOS **Setting:** not clearly stated (in Turkey)	N=20 anovulatory, infertile women with PCOS (oligo-menorrhea/amenorrhea and/or hirsutism, elevated LH/FSH ratio in postmenstrual phase, elevated serum androgens-testosterone and/or androstenedione- and typical US findings of multifollicules <9mm in diameter and hyperechogenic central stroma); no other infertility causes (complete infertility workup within previous 12 mo) All were CC-resistant (received previous CC therapy of max. 150mg/day on 5th-9th days of cycles for 3 mo and showed no evidence of ovulation based on luteal progesterone levels and US findings). **Group A:** n = 10 (mean age of 25.8±4.3 y; mean BMI of 24.4±6.7 kg/m^2 ; mean infertility duration of 2.4±1.6 y) **Group B:** n=10 (mean age of 27.3±2.8 y; mean BMI of 25.1±5.2 kg/m^2 ; mean infertility duration of 2.9±2.1 y) NSS difference in the clinical and endocrine features between groups	Patients randomly divided into 2 equal groups (*random number table*): **Group A** (odd numbered patients) treated with buserelin acetate nasal spray (GnRHa), 600 µg/day, for 6 wk before OI with HMG in conventional doses for 14 cycles. HMG started at 150 IU (2 ampoules) daily, increased by 1 ampoule every 4-5 days until adequate ovarian response (daily serum estradiol levels and US) achieved; dose continued until criteria for hCG administration (10,000 IU i.m.) reached (≥1follicle of >18 mm diameter; serum estradiol >150pg/mL per follicle>14mm diameter) **Group B** (even numbered patients) treated only with low-dose HMG for 17 cycles. HMG started at 75 IU i.m. daily, increased after 7 days to 112.5 IU per wk if no response; this increase in dose was continued to a max of 3 ampoules/day and if no ovarian response observed,patients considered unresponsive and treatment terminated; once ovarian response achieved, same dose continued until same criteria for hCG administration reached. Follicular response monitored with serial transvaginal US exams and serum estradiol levels	*Less multifollicular development and more monofollicular development in Group B than in Group A (17.6 vs. 57.1% and 70.6% vs. 35.7%; p<0.05) **Ovulation:** NSS difference in ovulation rate (P>0.05) *Ovulation rate (per cycle) was 78.5% in Group A and 76.5% in GroupB; **Pregnancy:** NSS differences in pregnancy rates (per patient and per cycle) between groups (P>0.05) *Pregnancy/patient rate of 40% in Group A (4 pregnancies) and 30% in Group B (3 pregnancies). *Pregnancy/cycle rate of 28.57% in Group A and 17.64% in Group B *Completed pregnancy rate of 75% (3/4) in Group A and of 66.6% (2/3) in group B **Delivery:** successful delivery achieved in all completed pregnancies; NSS difference in delivery rate (per patient) between groups; **Conclusion:** "Low-dose HMG has distinct advantages in eliminating multifollicular development and related complications in CC-resistant PCOS patients. The addition of GnRHa to gonadotrophins does not change the incidence of multifollicular development." "As a result of this study, we advocate low-dose gonadotropin therapy to prevent OHSS and multiple pregnancies."	**Miscarriages/Abortions:** *One abortion occurred in each group (NSS) **Multiple pregnancies:** *One twin pregnancy was detected in Group A (10%) and none in Group B (0%) (NSS) **OHSS:** *two cases of mild OHSS and 1 case of moderate OHSS were detected in 3 cycles in Group A (21.4%) and in none of Group B (0%)

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Table 3: Primary quantitative research studies (cont'd)

Study (authors, publication date, design, setting)	Study population	OI drug therapy	Reported results of interest* and Author(s)' conclusion	Reported complications and adverse events
Vegetti et al.,[68] 1998 **Design:** Randomized prospective pilot study conducted to evaluate effect of a 3-mo GnRHa (analog) in one cycle of OI with low-dose pFSH in CC-resistant patients with PCOS anovulation **Setting:** not clearly stated (in Italy)	N=20 patients (aged 26-32 y; BMI of 20-25 kg/m^2 ; basal LH of 4.5-16.4 mIU/ml) with PCOS (US scan showing an ovarian volume>10ml; at least 8-10 follicles of<10mm diameter; chronic anovulation with amenorrhea/oligoamenorrhea and midluteal progesterone <3.0ng/ml; acne and/or hirsutism; serum hyperandrogeneism and/or LH/FSH ratio of ≥2), CC-resistant (failed to ovulate or conceive after ≥6 mo of CC therapy, 100 or 200mg per day, from 3rd- 7th day of cycle) Four patients in Group A and 5 in Group B had never had gonadotrophin therapy (remaining patients treated after a wash-out of ≥4 mo after last gonadotrophin cycle). **Group A:** n=10 **Group B**: n=10 NSS differences in baseline homogeneity between groups	Patients were treated for single cycle and randomly assigned (*computer-generated scheme*) to: **Group A:** pFSH (Metrodin HP; Serono) in stepwise low-dose schedule: 75IU s.c. or i.m. daily until an ovarian follicle exceeded 14 mm in diameter; dose increased by 37.5 IU if no follicle >14mm at US scan on day 15 of stimulation, further increasing dose by 37.5 IU every week up to 4 weeks. If follicular growth occurred, hCG 5,000 (Profasi HP 5000; Serono) given when mean follicular diameter reached 18mm; hCG withheld when >5 follicles with >15mm diameter seen and serum 17β-estradiol >1,500 pg/ml; hCG withheld when>5 follicles with mean diameter of >15 mm seen and serum 17β-estradiol >1,500 pg/ml. **Group B:** 3 doses of GnRHa depot (decapeptyl 3.75 mg; Ipsen) i.m.; last dose administered in combination with first dose of pFSH (as for group A); all injections performed by one author (suppression confirmed by transvaginal US) Ovarian response monitored by US examinations of ovaries and serum estradiol assessments.	*Number of stimulation days and FSH units needed to achieve follicular growth were similar. **Ovulation:** *Nine cycles in Group A and 2 cycles in Group B (p<0.05) **Pregnancy:** *Five pregnancies in Group A (4 singleton and 1 twin) and no pregnancy in Group B (p<0.05) **Conclusion:** "Pretreatment with a 3-mo administration of a GnRHa did not improve the ovulation rate and pregancy rate in PCOS patient ovulation induction with low-dose pFSH" "This first pilot study using long-term GnRH combined with p-FSH in Clomiphene-resistant PCOS patients undergoing ovulation induction shows that adjunctive long-term GnRH-a therapy does not have a favourable impact on ovulation and pregnancy rates; this is also the reason why the study was interrupted".	**Multiple pregnancies:** *One twin pregnancy in Group A (20%). **Note:** no statement on miscarriage/abortion and/or incidence of OHSS observed in the women included

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Table 3: Primary quantitative research studies (cont'd)

Study (authors, publication date, design, setting)	Study population	OI drug therapy	Reported results of interest* and Author(s)' conclusion	Reported complications and adverse events
Muriana et al.,[54] 1999 **Design:** A randomized comparative study between OC/short term GnRHa and depot GnRHa protocols in women with CC-resistant PCOS **Setting:** not clearly stated (in Italy)	N= 30 women with PCOS (oligonemorrhea, LH/FSH ratio≥3, overt or borderline hyperandrogenemia, US appearance of polycystic ovary) who previously failed to conceive with CC therapy. All had physical examination, postcoital test and laparoscopy to rule out tubal infertility. Patients were randomly assigned to **Study group:** n=15 (mean age of 32.1±2.8 y; mean infertility duration of 4.2±2.1y; mean BMI of 27.8±1.1 kg/m^2) **Control group:** n=15 (mean age of 31.2 ±3.0y; mean infertility duration of 3.8±2.6 y; mean BMI of 28.4±1.0 kg/m^2) Patients in both groups matched for age, infertility duration, BMI values and baseline plasma hormone levels.	Patients randomly assigned (*method of randomization not stated)* to 2 pituitary down-regulation protocols: **Study group** received an OC for 21 days and a suspension triptoreline s.c. (Decapeptiyl, 0.1 mg, Ipsen S.p.a., Milan, Italy) until FSH administration (OC/short term GnRHa protocol); the 1st day of gonadotrophin coincided with the 4th day after end of OC in ~90% of women **Control group** received depot triptoreline (Decapeptyl 3.75 mg; Ipsen S.p.a., Milan, Italy) at beginning of follicular phase (depot GnRH protocol). Progesterone in oil, 50mg daily (Prontogest, Amsa s.r.l., Rome, Italy) was given to support luteal phase. In both groups FSH (Metrodin HP, Serono S.p.a., Rome, Italy) adminsitered at starting daily dose of 150 IU for 5 days; then adjusted until hCG (ProfasiHP, 5,000 IU, Serono S.p.a., Rome, Italy) administration (when ≥ 2 follicles measured 16 mm in diameter and estradiol exceeded 200pg per follicle). Vaginal US follicle measurements and plasma estradiol levels were used for monitoring the treatment effect.	*Both regimens gave similar results in terms of days of FSH administration, immature follicles, and preovulatory follicles, and hormone levels on hCG administration **Pregnancy:** *The pregnancy rate was similar in both groups (5 pregnancies in Study group and 5 pregnancies in Control group) **Delivery:** *No differences found in the number of term deliveries between groups *In Study group there were 5 deliveries: 2 sets of twins and 3 singletons; *In the Control group there were 4 deliveries: 2 singletons, 1 set of triplets (cesarian section) and 1 set of twins **Conclusion:** "The OC/short term GnRHa protocol reduced both GnRHa dosage and FSH requirements and it was as effective as depot GnRHa regimen to prevent spontaneous mid cycle LH surge." "Further studies on the duration of recovery phase after GnRHa administration and larger sample size are needed to confirm these data and to modify the strategies of GnRHa use in ovulation induction".	**Miscarriages/Abortions:** *No difference was found between groups in terms of incidence of abortions *One of the triplet pregnancy in the Control group terminated in late abortion at 22 wks. **Multiple pregnancies:** *There were 2 sets of twins in the Study group. *There were two sets of triplets and one set of twins in the Control group. **OHSS:** *No difference was found between groups in terms of incidence of OHSS

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Table 3: Primary quantitative research studies (cont'd)

Study (authors, publication date, design, setting)	Study population	OI drug therapy	Reported results of interest* and Author(s)' conclusion	Reported complications and adverse events
Homburg et al.,[88] 1995 **Design:** Double blind, placebo controlled RCT conducted to explore effect of co-treatment with rGH and GnRHa and HMG for OI in women with CC-resistant PCOS **Setting:** not clearly stated (in Israel)	N= 30 women (12 obese) with anovulatory infertility associated with PCOS (oligo-menorrhea, amenorrhea, typical US findings, and/or hirsutism); all were CC-resistant (failed to ovulate in doses up to 200mg/day for 5 days) All had normal hysterosalpingography and partner's sperm parameters. **GH group:** of n=15 (mean age 29.8±4.3 y; mean infertility duration 4.3±2.3 y; 7 with primary infertility and 8 with secondary infertility, mean BMI 25.6±4.6 kg/m^2) **Placebo group:** of n=15 (mean age 28.5±4.7 y; mean infertility duration 3.3±1.6y; 6 with primary infertility and 9 with secondary infertility, mean BMI 26±5.1 kg/m^2) *NSS difference in basal clinical and laboratory data between groups.	All women recruited were *computer randomized* to receive either human GH or placebo for single cycle. All women received GnRHa in form of DTRP6 (Decapeptyl CR: 3.75 mg microcapsules, i.m., Ferring, Malmo, Sweden) at a random time in the amenorrheic and 3 wk following menstruation in oligomenorrheic patients. *Two wk later, following confirmation of pituitary down-regulation by measurement of FSH and LH levels and ovarian quiescence by US and estradiol levels<25pg/mL, treatment with HMG (Pergonal, Teva, Petah Tikva, Israel) initiated (individually adjusted dose scheme); hCG (10,000 IU; Chroigon: Teva) administered i.m. when ≥ 1 follicle of>16mm seen on US and estradiol concentrations were in range of 500-2000 pg/mL(1350-5400 pmol/l). Luteal phase support given given on days 3,7, 11 following hCG using progesterone Patients received human GH administered in doses of 12 IU/day i.m. for 7 days from the first day of HMG administration **(GH group)** or placebo (administered in the same fashion) **(placebo group).**	*Number of ampoules, duration of treatment and daily effective dose of HMG required to achieve ovulation were NSS different between groups **Ovulation:** *All but one patient in each group ovulated. **Pregnancy:** *In all, 7 clinical pregnancies achieved: 3 in GH group and 4 in placebo group. **Delivery:** *In all 3 deliveries were achieved: 1 in GH group and 2 in placebo group. **Conclusion:** "We conclude that although GH kinetics are abnormal and GH pituitary reserves generally low in women with PCOS, adjuvant GH treatment to GnRHa/HMG does not influence follicular development or sensitivity in response to gonadotrophins and that it does not seem likely to be of any potential clinical benefit for the treatment of PCOS." "Clearly no firm conclusions may be drawn regarding any influence of additive GH on pregnancy rate in this group of patients as that would require a sample size of a further 126 recruits to have 80% chance of detecting an increase in pregnancy rate from 27 to 50%. In the light of our initial results and the resulting points raised in the discussion, an extension of the trail does not appear justified".	**Miscarriages/Abortions:** *In all, 4 miscarriages occurred (2 in each group). **Multiple pregnancies:** *One delivery of twins in the placebo group. **OHSS:** *No OHSS cases observed.

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Table 3: Primary quantitative research studies (cont'd)

Study (authors, publication date, design, setting)	Study population	OI drug therapy	Reported results of interest* and Author(s)' conclusion	Reported complications and adverse events
George et al., [111] 2003 **Design:** randomized, controlled trial conducted (between 1999 and 2001) to compare efficacy of sequential treatment with metformin and CC with conventional gonadotrophins as hMG. **Setting:** reproductive medicine unit of Medical College (in Southern India)	N=60 infertile women with PCOS (clinical features of oligomenorrhea and hyperandrogenism, along with either biochemical abnormalities of a raised LH/FSH ratio or LH or US feature of PCO) and CC resistance (failure to ovulate to a dose of 200mg/day for 5 days) All women had normal liver, renal and thyroid function and glucose tolerance and prolactin levels. Excluded were women with associated tubal or male factor infertility and those with BMI >35 kg/m^2. All women instructed to maintain lifestyle. **Group I** = 30 women (age of 25.1±3 y; BMI of 25.5±3.7 kg/m^2) **Group II** = 30 women (age of 26±2.9y; BMI of 24.6±2.6 kg/m^2)	All women randomized (*block randomization using RALLOC software, with concealment allocation by use of opaque envelopes*) to receive **Group I:** metformin 1500 mg/day in 3 doses for 6 mo; each woman given tablets for 30 days and reviewed at 30 day interval (compliance and side effects); at 6 mo, clinical and biochemical parameters re-checked; CC (150 mg/dat) re-started after 6 mo in combination with metformin; when leading follicle >20 mm, hCG (5000 IU) administered to induce ovulation; CC dose increased to 200mg/day if women did not ovulate on 150mg/day; 3 cycles with ovulatory dose were planned; **Group II:** HMG (low-dose, step-up regimen), with intention to treat for at least 3 cycles; starting dose of 75 IU, on day 5 of spontaneous/induced cycle; dose increased by 75 IU every 7-10 days if no ovarian response (no follicle> 10 mm on US); when follicular development started, same dose maintained until leading folluicle >18mm and hCG (5000) administered to induce ovulation; clinical and biochemical evaluation after treatment if women did not conceive; Follicular monitoring by US; SHBG levels measured by immunoradiometric assay; T level, DHEAS and insulin levels measured by radioimmuno assays; FSH and LH measured by immuno assays. **Note:** in Group I: 27 women completed treatment; 3 discontinued metformin at 3 mo (wanted quicker results); in Group II: 27 women completed treatment and had 50 cycles of OI (3 dropped out due to financial constraints; NSS difference between characteristics of these women and those who completed treatment);	Groups did not differ in anthropometric or biochemical values. **Ovulation:** Group I: SS improvement ($p<0.001$) in ovulation with metformin-CC; 14 women ovulated (46.7%); Group II: 39 cycles had ovulation (43%); in 11 cycles women discontinued HMG due to poor response and inability to continue **Pregnancy:** NSS difference between groups (95% CI, -13% and 26.2%) Group I: cumulative 6 mo pregnancy rate of 16.7% (1 woman conceived during metformin and 4 women conceived during metformin-CC) Group II: cumulative 6 mo pregnancy rate of 23.3% (7 women conceived) **Delivery** Group I: 2 normal deliveries Group II: 6 normal deliveries **Conclusion:** "Sequential treatment with metformin and clomiphene citrate is an effective and safe option for clomiphene-resistant women with PCOS."	**Miscarriages/Abortions:** There were 2 missed abortions, one in each group. **Note:** no statement on presence/absence of multiple pregnancies or OHSS observed in the women included. **Other adverse events:** There was one ectopic pregnancy and one intrauterine death at 28 weeks in Group I. **Side effects:** Three women in Group I had mild side effects: transient nausea, and vomiting (reduced metformin dose to 1000 mg/day for 2 wks)

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Table 3: Primary quantitative research studies (cont'd)

Study (authors, publication date, design, setting)	Study population	OI drug therapy	Reported results of interest* and Author(s)' conclusion	Reported complications and adverse events
Ramzy et al., [112] 2003 **Design:** open labeled randomized controlled trial conducted to investigate the potential value of metformin prior and concomitent with CC and its impact on improving ovulation rate and cycle regularity in overweight and lean women with PCOS (March 2001 to Nov. 2002) **Setting:** Outpatient clinic of gynecology of an university hospital (in Egypt)	N= 60 women complaining of anovulatory infertility and diagnosed with PCOS (PCO on vaginal US: >8 subcapsular follicles of 3-8mm diameter in one plane in one ovary and increased stroma; and at least one of the following: oligomenorrhea, or amenorrhea, hirsutism – Ferriman Gallwey score> 7 – or acne); Excluded were: patients with bilateral tubal block, organic uterine or ovarian pathology, hyperglycemia or infertile semen analysis of their husbands; hypo-/hyperthyroidism, hyper-prolactinemia and those with Cushing syndrome. **Group I:** 30 women with BMI >28 **GroupII:** 30 women with BMI <28	Each of the Group I and Group II was further subdivided to subgroups: Subgroup A: n=15 patients given metformin 500 mg (Metformin HCl; Chemical Industries Development, Giza, Egypt) for 6 wk prior to CC therapy (50 mg tablet; Clomid; Global Napi Pharmaceuticals under license of Hoechst Marion Roussel France) for 3 cycles (dose of 100 to 250 mg daily according to BMI and previous response, starting 2nd day of normal or progestin withdrawal bleeding cycle for 5 days) and continued throughout induction Subgroup B: n=15 patients given placebo (vitamine B complex; the Alexandria Co. For Pharmaceuticals. Alexandria – Egypt) instead of metformin The hCG (10,000 IU; Pregnyl, NV Organon . International, The Netherlands) was administered via intramuscular single injection when leading follicle was 20 mm in diameter. OI repeated for all patients for 3 cycles in addition to metformin or placebo using same dose or increasing it according to response. Both subgroups compared in terms of BMI, biochemical criteria, cycle regularity, and success of ovulation induction before and 6 wk after taking metformin/placebo. Transvaginal US serial folliculometry used to check ovulation.	**Ovulation:** SS difference between the 2 subgroups of Group I and Group II in in cumulative response (after 3 cycles): Subgroup I-A vs. Subgroup I-B: 73.3% vs. 13.3 % cumulative response (p=0.003) Subgroup II-A vs. Subgroup II-B: 86.6% vs. 40% (p=0.001) NSS difference between successful ovulation inductions in the 1st cycle in the 2 subgroups of Group II **Pregnancy:** No conception occurred in Group I or in Group II. **Conclusion:** "…significantly higher successful ovulation induction rates can be achieved with the use of metformin (prior to and as an adjuvant to clomid) both in overweight and lean women with polycycstic ovarian syndrome."	**Note:** no statement on presence/absence of miscarriages/abortions, multiple pregnancies or OHSS observed in the women included

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Table 3: Primary quantitative research studies (cont'd)

Study (authors, publication date, design, setting)	Study population	OI drug therapy	Reported results of interest* and Author(s)' conclusion	Reported complications and adverse events
Ghazeeri et al.,[94] 2003 **Design:** Double-blind randomized placebo-controlled trail, conducted to investigate investigated the effect of rosiglitazone maleate on ovulation induction in overweight and obese, CC-resistant women with PCOS recruited from a university based infertility practice. The duration of the study was 2 months **Setting:** Academic reproductive endocrinology clinic (in USA)	N= 25 women with PCOS (anovulation with P_4- <5.0 ng/mL; oligomenorhhea with no spontaneous menses in last 60 days; positive menstrual response to progestin withdrawal test; and either self-reported hirsutism or total T>65 ng/mL) who had to have BMI >26kg/m^2; failed to ovulate after CC (150 mg/day) and wanted to become pregnant. Subjects excluded: if pregnant; suffered from diabetes or had a fasting serum glucose >125 mg/dL; had congenital adrenal hyperplasia or a fasting serum 17-∝-OHP >200ng/dL; had thyroid disease, hyprolactinemia, congestive heart failure, hypertension, or hepatic or renal dysfunction. Also excluded were those who had any OI agent or oral hypoglycemic agent within last 30 days of enrollment 30 women were screened and 25 randomized into **Group I** = 12 women (age of 28.7±3.5 y; parity of 0.1±0.3; BMI of 35.5±4.9 kg/m^2) **Group II** = 13 women (age of 28.7±4.1y; parity of 0.2±0.4; BMI of 38.5±7.5 kg/m^2)	All women received a 10 day course of 10 mg/day MPA (Pharmacia and Upjohn, Peapack, NJ) and started rosiglitazone (Avandia®, Glaxo SmithKline Pharmaceuticals, Philadelphia, PA), 4 mg b.i.d. Subjects then randomized (*allocation sequence generated from random number table;assigned through consecutively numbered opaque sealed envelopes*) into **Group I:** For cycle 1: continued rosiglitazone 4mg b.i.d.; started on day 5 taking a placebo capsule/day for 5 days; For cycle 2: repeated the same regim. **Group II:** For cycle 1: continued rosiglitazone 4 mg b.i.d.; started on day 5 taking a capsule of CC 50mg/day, for 5 days; For cycle 2: continued rosiglitazone and increased dose of CC to 100mg/day for 5 days, starting day 5. **For all subjects** cycle 1 began with subject's withdrawal menses; Ovulation determined by serum P_4 measurement on cycle days 21, 24, 28; if ovulation occurred rosiglitazone discontinued and subject proceeded study's exit investigations; those without ovulation by cycle day 28, continued rosiglitazone and then given another MPA withdrawal menses to initiate cycle 2. Ovulation measurements repeated same way. On 28 day of 2nd cycle all subjects had hormone assays, lipoproteins, liver and renal function tests; subsequently exited study. The investigators, study personnel, and patients were blinded to their assignments. **Note:** Only 22 subjects completed study: 2 subjects in Group I and 1 in Group II were lost to follow-up. None ovulated and they were included in the ovulation rate analysis.	The two groups did not differ in age, parity, BMI, glucose to insulin ratio, total T, total cholesterol and HDL and LH levels, or SHBG **Ovulation:** *Overall, 14/25 (56%) women, who were previously resistant to CC, successfully ovulated. *In subjects taking rosiglitazone alone (Group I), 4 of 12 (33%) subjects ovulated compared with 10 of 13 (77%) women randomized to rosiglitazone with CC (Group II) (P=.04, Fisher's exact). **Pregnancy:** *One subject in Group I became pregnant, resulting in one uncomplicated live birth; two subjects in Group II conceived, with one successful live birth. **Conclusion:** Short-term rosiglitazone therapy enhances both spontaneous and clomiphene-induced ovulation in overweight and obese women with PCOS. Rosiglitazone therapy improves insulin sensitivity and decreases hyperandrogenemia primarily through increases in SHBG.	**Miscarriages/Abortions:** One first trimester, spontaneous abortion in Group II **Note:** No statement on presence/absence of multiple pregnancies or OHSS **Adverse events:** *One subject complained of swollen fingers and another of mild headaches. A SS decrease in hematocrit was observed after completion.

* - Reported results of interest included: multifollicular development, ovulation rate, and pregnancy, live birth, and/or delivery rates.

Table 4: Indications of methodological quality of the primary research studies reviewed

Study	Criteria for determining methodological quality							Comments on methodological quality (limitations and weaknesses)	Reported outcomes of interest (type and definition, and how they were measured/diagnosed)
	A	B	C	D	E	F	G		
Timmerman-van Kessel et al.,[107] 2000	?	?	?	?	?	✗	✓	•Method of randomization not clearly stated; not clear on the adequacy of concealment of treatment allocation; multicentre centre (only 1 centre mentioned as setting); parallel design; small sample size; no blinding performed; no statement on whether intention to treat analysis was done; two women dropped out and did not receive treatment in CC group (their characteristics and reasons not described) and they were excluded from analysis and were not kept in their original group; no description on sample size calculation provided; information on compliance not provided/discussed; duration, timing of trial not stated; •Description of study patients was incomplete (no information on BMI and tubal patency) •Selection of study population and inclusion/exclusion criteria not clearly described/defined; •OI regimen defined but description was inadequate (no clear information on follow-up period; whether patients had co-interventions or not; or who administered the OI therapy); •Statistical significance and CIs not reported for outcomes of interest (however, median and inter-quartile ranges were presented graphically); •Patients' complication profile not described adequately	•Main outcome measures: serum concentrations of E_2, LH, and FSH (assessed before treatment was started and after each ovarian sonography). •Ovulation rate per initiated cycle, and pregnancy rate per initiated cycle reported for both groups. •ovulation rate per patient and pregnancy rate per patient were reported for the CC group. •ovulation assumed by disappearance of the dominant follicle on vaginal US and a subsequent increase in serum P (>10nmlo/L) •pregnancy tests were performed 16 days after ovulation by determination of beta-hCG in the uterine and serum
Hassan et al.,[108] 2001	?	?	?	?	?	?	?	•Not clear on adequacy of concealment of treatment allocation; single centre, parallel design; no blinding performed; no statement on whether intention to treat analysis was done; 14 women dropped out and were excluded from analysis (characteristics and/or reasons not described); no description on sample size calculation; compliance not discussed; duration, timing of trial not stated; •Description of study patients was incomplete (information on age, BMI, infertility duration, parity, PCOS diagnosis, tubal patency, and details on infertility work up not provided) •Selection of study population and inclusion/exclusion criteria not clearly defined/described; •Descrition of OI regimen defined inadequate (not clear whether patients had co-interventions or not; or who administered OI therapy); •Statistical significance and CIs not reported for outcomes of interest; •Patients' complication profile not described adequately (information on OHSS not stated) •Study limitations not described; implications for practice and research not discussed	•Main outcome measures were incidence of clomiphene resistance, monofollicular response, fasting insulin/glucose ration, serum testosterone, and clinical pregnancy rates (per patients) •Cardiac pulsation rate (per patient) was also reported. •method of detecting responsiveness to CC therapy in terms of ovulation not clearly stated •method of clinical pregnancy diagnosis was not stated

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Table 4: Indications of methodological quality of the primary research studies reviewed (cont'd)

Study	Criteria for determining methodological quality							Comments on methodological quality (limitations and weaknesses)	Reported outcomes of interest (type and definition, and how they were measured/diagnosed)
	A	B	C	D	E	F	G		
Parsanezhad et al.,[109] 2002	?	?	?	?	✓	?	?	*Method of randomization not stated; not clear on adequacy of concealment of treatment allocation; single center study; parallel design; no information on how blinding was performed; no assessment of adequacy of blinding performed; no statement on whether intention-to treat analysis was done; no description of sample size calculation; compliance not discussed; timing of study not stated; *description of the subjects was incomplete (no information on parity) *selection of study population and inclusion/exclusion criteria not adequately described; *OI regimen not adequately described (not clear who administered the treatment or whether patients had co-interventions or not; follow-up period not clearly defined); *Patients' complication profile not adequately described (stated only midl effects) *No adequate discussion on implications for practice and research of the reported results was provided	Main outcomes: follicular development, hormonal changes, ovulation rate, pregnancy rate *ovulation evidenced by P levels of >5 ng/mL in mid-luteal phase *method of pregnancy diagnosis not mentioned

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Table 4: Indications of methodological quality of the primary research studies reviewed (cont'd)

Study	Criteria for determining methodological quality							Comments on methodological quality (limitations and weaknesses)	Reported outcomes of interest (type and definition, and how they were measured/diagnosed)
	A	B	C	D	E	F	G		
Hugues et al. [110] 1996	?	?	?	?	?	✓	?	•Method of randomization not stated; no details on concealment of treatment allocation; single centre; parallel design; no description on sample size calculation; blinding not performed; no statement on whether intention to treat analysis was done; 4 women did not complete study and were not included in analysis (no information on their characteristics); possibility of attrition bias not discussed; primary outcomes not explicitly stated and defined/described; no information on compliance; duration, timing and setting of trial not stated clearly; •Inadequate description of study patients (information on parity not provided) •Selection of study population and inclusion/exclusion criteria not clearly defined/described; •Inadequate description of OI regimen (no clear information on follow-up period; not clear number of cycles – started and/ or completed- per patient; not clear whether patients had co-interventions or not or who administered OI therapy) •Confidence intervals for outcomes of interest not reported •No adequate discussion on implications for practice and research of reported results	•Outcomes of treated cycles included: luteal oestradiol and luteal progesterone levels, number of OHSS per group, number of pregnancies per group, number (%) of miscarriages per group; number of ongoing pregnancies per group •Method of pregnancy diagnosis was not stated •Method used to document clinical OHSS was not described or stated.

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Table 4: Indications of methodological quality of the primary research studies reviewed (cont'd)

Study	Criteria for determining methodological quality							Comments on methodological quality (limitations and weaknesses)	Reported outcomes of interest (type and definition, and how they were measured/diagnosed)
	A	B	C	D	E	F	G		
Lidor et al.,[75] 2000	?	?	?	?	?	?	✓	*Method of randomization not stated; not information on allocation concealment; single centre, parallel design; small sample size; no blinding performed; no statement on whether intention to treat analysis was done; it appears that no exclusions had taken place and all randomized patients were included in analysis; no information on sample size calculation; location of trial not stated clearly; no information on compliance was; duration, timing of trial were not stated; *Description of study patients was incomplete (details on infertility work up, and information on tubal patency and partners' semen analysis and BMI values not provided; criteria for PCOS diagnosis not stated) *Selection of study population and inclusion/exclusion criteria not clearly defined/described; *OI regimen description was inadequate (no clear information on follow-up period; not clear whether patients had co-interventions or not or who administered OI therapy); *Statistical significance and CIs not reported for outcomes of interest; *Patients' complication profile not described adequately; *Study limitations were not adequately described and discussed.	*Main outcome measure was premature luteinization defined as serum progesterone >1.5 ng/mL before hCG administration. *Pregnancy rate (per patient) was also reported. *method of pregnancy diagnosis was not stated
Ergur et al., 1998[86]	?	?	?	?	✓	✓	?	*Single centre, parallel design; small sample size; no blinding performed; no statement on whether intention to treat analysis was done; it appears that no exclusions had taken place and all randomized patients were included in analysis and kept in their original groups; no description of sample size calculation; location of trial not stated clearly; no information on compliance; duration, timing of trial were not stated; *Description of study patients was incomplete (no information on parity) *Selection of study population and inclusion/exclusion criteria not clearly defined/described; *OI regimen description was inadequate (no clear on follow-up period; number of cycles per patient; co-interventions; or who administered OI); *CI for the outcomes of interest were not reported; *Study limitations not described; inadequate discussion of implications.	*All cycles compared in terms of number of follicles per cycle, cycles human chorionic gonadotropin withheld, estradiol level on ovulation day, treatment duration and number of ampules used per cycle. *OHSS, multiple pregnancy, ovulation rate (per cycle), pregnancy rate (per cycle and per patient), delivery rate (per pregnant patient) were also reported *Ovulation was defined by a midluteal progesterone level of >30nmol/L and by US *pregnancy defined by a rise in β-hCG and sonographic evidence of gestational sac *completed pregnancy not defined

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Table 4: Indications of methodological quality of the primary research studies reviewed (cont'd)

Study	Criteria for determining methodological quality							Comments on methodological quality (limitations and weaknesses)	Reported outcomes of interest (type and definition, and how they were measured/diagnosed)
	A	B	C	D	E	F	G		
Vegetti et al., [68] 1998	?	?	?	?	✓	?	?	•Single centre, parallel design; small sample size; no details on sample size calculation; blinding not performed; no information on number of patients/cycles initially included, excluded and analyzed; no statement on whether intention to treat analysis was done; it appears that no exclusions had taken place and all randomized patients were included in analysis and kept in their original groups; no information on compliance; duration, timing and location of trial not stated clearly; •Inadequate description of study population (no information on infertility duration and parity); •Selection of study population not adequately described; •OI regimen description was inadequate (no clear information on whether patients had concomitant medication or not and on follow-up period; not clear number of cycles – started and/or completed- per patient; or who administered OI therapy); •Patients' complication profile not described adequately (no information on miscarriages/abortions and incidence of OHSS); •No adequate discussion on the clinical importance of reported results.	•Outcome evaluation based on rate of ovulatory cycles, rate of monofollicular cycles and serum plasmatic estradiol levels on the day of hCG. •Reported ovulatory cycles per group (defined by serum progesterone levels of >8 ng/ml); •Ovulation was confirmed by serum progesterone determinations performed 8 days after hCG injection by EIMA assays, Ares Serono, Switzerland); •Reported number of pregnancies achieved per group was reported; •Method of pregnancy diagnosis was not stated.
Muriana et al., 1999 [54]	?	?	?	?	✓	✓	?	•Method of randomization not stated; not clear on adequacy of concealment of treatment allocation; single centre, parallel design; small sample size; no blinding performed; no statement on whether intention to treat analysis was done; it appears that no exclusions had taken place and all randomized patients were included in analysis and kept in their original groups; no description on sample size calculation; location of trial not stated clearly; no information on compliance; duration, timing of trial were not stated; •Description of study patients was incomplete (no information on parity and partners' semen analysis); •Selection of study population and inclusion/exclusion criteria not clearly defined/described; •OI regimen description was inadequate (no clear information on follow-up period or who administered therapy); •Study limitations were not adequately described and discussed; no discussion/conclusion on the effect of the 2 protocols on clinical outcomes;	•The outcomes considered were mean FSH dosage, days of stimulation, plasma hormone levels, follicles, cancellations, pregnancies, abortions, deliveries •method of clinical pregnancy diagnosis was not stated.

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Table 4: Indications of methodological quality of the primary research studies reviewed (cont'd)

Study	Criteria for determining methodological quality							Comments on methodological quality (limitations and weaknesses)	Reported outcomes of interest (type and definition, and how they were measured/diagnosed)
	A	B	C	D	E	F	G		
Homburg et al.,[88] 1995	?	✓	?	?	?	✓	✓	*Not clear on adequacy of concealment of treatment allocation; single centre, parallel design; no description of the double-blinding; assessment of adequacy of blinding not performed; no statement on whether intention to treat analysis was done; no description on sample size calculation; primary outcomes not explicitly defined/described; location of trial not stated clearly; no information on compliance; duration, timing of trial not stated; *Selection of study population and inclusion/exclusion criteria not clearly defined/described; *OI regimen description was inadequate (no clear information on follow-up period; not clear on number of cycles per patient; whether patients had co-interventions or not; or who administered OI therapy); *Completed participation was not defined *Statistical significance and CI not reported for outcomes of interest;	*Treatment results measured in terms of number of ampoules, duration of treatment and daily effective dose of HMG required to achieve ovulation, serum etradiol concentrations and number of follicles induced, ovulatory cycles per group, number of clinical pregnancies per group, number of miscarriages per group, and number of deliveries (singletons/twins) per group. *Ovulation defined by midluteal phase serum progesterone concentrations and US examination. *method of clinical pregnancy diagnosis not stated
George et al.,[111] 2003	?	?	?	?	✓	?	✓	*Single center study; parallel design; relatively small sample size; no blinding; intention-to-treat stated; compliance not discussed; *Incomplete description of the subjects (no information on duration of infertility and parity); *Biochemical inclusion criteria not specifically defined; *OI regimen description was inadequate (not clear who administered OI therapy); *Patients' complication profile not adequately described (only mild side effects mentioned for the metformin group).	Main outcomes included: cumulative pregnancy rate (per patient) and ovulation rate per patient; *no clear definition stated for detecting ovulation *method for pregnancy diagnosis was not stated

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Table 4: Indications of methodological quality of the primary research studies reviewed (cont'd)

Study	Criteria for determining methodological quality							Comments on methodological quality (limitations and weaknesses)	Reported outcomes of interest (type and definition, and how they were measured/diagnosed)
	A	B	C	D	E	F	G		
Ramzy et al.,[112] 2003	?	?	✓	?	✓	✕	✓	·Not clear when randomization (done on alternate numbers) was performed; not clear on adequacy of concealment of treatment allocation; single center study; parallel design; small sample size; no blinding; not statement on whether intention-to-treat was intended/done; no description of sample size calculation; compliance not discussed; ·Description of the subjects was incomplete (no information on parity and infertility duration); ·OI regimen not adequately described (not clear who administered the treatment; not clear whether patients had co-interventions or not; adjustment criteria was not clear; no information on completed participation); ·No information on presence/absence of miscarriage, multiple pregnancy and/or OHSS.	Main outcomes; ovulation rate and regularity of the cycle ·success of ovulation induction monitored by transvaginal US on 8th day of cycle and every 2 days ·method of pregnancy diagnosis not mentioned
Ghazeeri et al.,[94] 2003	?	?	✓	?	?	?	✓	·Single center study; parallel design;small sample size; no statement on whether intention to treat was done; 3 women were lost for follow-up (their characteristics not described) but they were included in the analysis on ovulation rate; timing of study not stated; no information on compliance; ·Description of subjects was incomplete (no information on duration of infertility, presence of other type of infertility, tubal patency, partner's semen analysis); ·OI regimen not adequately described (not clear who administered the treatment; not clear whether patients had co-interventions or not; follow-up period not clearly defined); ·Statistical significance and CI not reported for all outcomes of interest; ·Patients' complication profile not adequately described (only mild side effects mentioned)	Primary oiutcome was ovulation defined by a serum P_4 >5.0 ng/mL in either treatment cycle Secondary outcomes included pregnancy and changes in Secondary outcomes were pregnancy and changes in insulin sensitivity, serum lipoproteins, and androgens, and hepatic and renal function with rosiglitazone therapy ·method of pregnancy diagnosis not mentioned

✓ adequate information (gcod)

? some information or incomplete information (moderate to poor)

✕ no information

Table 5: Systematic reviews and meta-analyses

Study (authors, publication date, place)	Study's characteristics	Study's main findings and conclusions
Bayram et al., [113] 2001 (update) Cochrane Menstrual Disorders and Subfertility Group, The Cochrane Collaboration Amsterdam, The Netherlands	•This is an update of a systematic review conducted to assess the effectiveness of GnRH use in women with CC-resistant PCOS, in terms of ovulation induction, pregnancy, miscarriage, multiple pregnancy and OHSS; •The search strategy of the Menstrual Disorders and Subfertility review group was used •Included were RCTs that dealt with use of GnRH for OI in women with PCOS and contained a control group. Non-RCTs were included only if treatment consisted of GnRH vs. another treatment used for OI in subfertile women with PCOS. •An electronic MEDLINE and EMBASE search was conducted (*time periods are not clearly identified in this published document).* The reference lists of all studies found were checked for relevant trials. •Two reviewers extracted relevant data independently and differences of opinion were registered and resolved by consensus with the senior author. •All trials were screened and analyzed using predetermined quality criteria. Validity was assessed in terms of certain quality criteria including method and timing of randomization, duration and completeness of follow-up, presence or absence of cross-over and co-intervention, whether pregnancy was a measured outcome; how pregnancy results were reported; and the source of funding. •Data were extracted in 2X2 tables, generated for all relevant outcomes. ORs were generated using the Peto modified Mantel-Haenszel technique.	•Three RCTs and one non-randomised comparative trial were included. The OR for ovulation rate was 16 (95 % CI: 1.1-239) in the study comparing GnRH and FSH with FSH. When GnRH after GnRHa pre-treatment was compared with GnRH after oral contraceptive pre-treatment, an OR of 7.5 (95 % CI: 1.2-46) was obtained. •The four trials were small and of too short duration to show any significance in pregnancy results: per study only 1 to 4 pregnancies occurred. Multiple pregnancies were not seen. OHSS was seen only in patients stimulated with HMG. •The few published controlled studies with pulsatile GnRH are small, of short duration and follow-up and of low quality. No conclusions can be drawn on the efficacy/effectiveness of pulsatile GnRH in women with PCOS or with CC-resistant PCOS. •Combined results obtained from uncontrolled case-series indicate that pulsatile GnRH can be effective in women with CC-resistant PCOS, although much less so than in women with hypothalamic amenorrhea. They also suggest that effectiveness of pulsatile GnRH is probably enhanced by pre-treatment with a GnRHa. •If one considers the effort of the procedure, the area of indication is expected to be small. •New studies with pulsatile GnRH are unlikely to be performed.

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Table 5: Systematic reviews and meta-analyses (ont'd)

Study (authors, publication date, place)	Study's characteristics	Study's main findings and conclusions
Nugent et al.,[59] 2001 (update) Cochrane Menstrual Disorders and Subfertility Group, The Cochrane Collaboration Leeds, United Kingdom	•This is an update of a systematic review conducted to determine the effectiveness of urinary-derived gonadotrophins as OI agents in patients with PCOS trying to conceive. In particular, to assess the effectiveness of (1) different gonadotrophin preparations, (2) the addition of a GnRHa to gonadotrophin stimulation and (3) different modalities of gonadotropnin administration. •The search strategy consisted of (1) the search strategy developed for the Menstrual Disorders and Subfertility Group as a whole; trials were identified from the Group's Specialised Register of Controlled Trials; (2) additional specific electronic MEDLINE searches(MESH and text words: polycystic ovary syndrome, PCO, reproduction techniques, menotrophin, gonadotrophin, FSH, hMG); and (3) bibliographies of identified studies and narrative reviews. •Selected were only RCTs in which urinary-derived gonadotrophins were used for induction of ovulation in patients with primary or secondary subfertility attributable to PCOS. •Two authors extracted the data independently. The following criteria were assessed: (1) the methodological characteristics of the trials, (2) the baseline characteristics of the studied groups and (3) the outcomes of interest: pregnancy rate (per cycle), ovulation rate (per cycle), miscarriage rate (per pregnancy), multiple pregnancy rate (per pregnancy), overstimulation rate (per cycle) and OHSS rate (per cycle). •Where suitable, meta-analysis was performed using Peto's OR with 95% CI with the fixed effect Mantel-Haentszel equation.	•The results of the 14 reviewed RCTs showed: - no significant differences in the outcomes studied when different treatment modalities were compared; - a demonstrable benefit of uFSH preparations when compared to HMG preparations in terms of a reduced risk of OHSS in cycles when administered without concomitant use of a GnRHa (OR 0.20; 95% CI 0.08-0.46); - a higher overstimulation rate when a GnRHa is added to gonadotrophins (OR 3.15; 95% CI 1.48-6.70) without a significantly higher OHSS rate (OR 1.41; 95% CI 0.50-3.95); - there were insufficient data to draw conclusions on miscarriage and multiple pregnancy rates; and •All 14 RCTs were small to moderate size, their methodological quality was generally poor, and only few dealt with the same comparisons. Any conclusions, therefore, remain tentative as they are based on a limited amount of data and require further RCTs to substantiate them. •There was a trend towards better pregnancy rates with the addition of a GnRH-a to gonadotrophin stimulation and these interventions warrant further study. •The reduced incidence of OHSS with the use of uFSH compared to HMG needs to be balanced against the additional financial costs involved. A higher overstimulation rate with addition of a GnRHa to gonadotrophins means that their routine use is unjustified at present. Further RCTs of better methodological quality are required to substantiate the tentative findings from this review with more considence."

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Table 5: Systematic reviews and meta-analyses (cont'd)

Study (authors, publication date, place)	Study's characteristics	Study's main findings and conclusions
van Wely et al. [116] 2003 Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Academic Medical Center, University of Amsterdam, The Netherlands	•This paper is based on a Cochrane review published in The Cochrane Library, issue 2, 2001 (see www.CochraneLibrary. net for information) with permission from The Cochrane Collaboration and Update Software. •This is a systematic review performed to study the efficacy and safety of rFSH vs. uFSH and to compare different dose regimens of rFSH for OI in women with CC-resistant PCOS. •The review has drawn on the search strategy developed for the Cochrane menstrual Disorders and Subfertility Group as a whole. Relevant trials were identified from the Trial Register of the Review Group and electronid searches of MEDLINE and EMBASE. Keywords used: polycystic ovary syndrome, oligomenorrhoea, oligo-menorrhoea, amenorrhoea, anovulation, ovulation induction, recombinant FSH and FSH. Hand-searching of references in the slected trials was performed and citations lists of eligible studies, conference abstracts and relevant review articles were examined as well. Serono Benelux BV and NV Organon (manufactui=rers of Gonal F® and Puregon® were asked for ongoing studies and upublished data. •Only RCTs comparing rFSH and uFSH or different treatment modalities of rFSH for OI in women with PCOS and specifying at least the clinical pregnancy rate per woman were eligible for review. The selection was performed independently by 2 reviewers. Same reviewers independently extracted data (entered in RevMan 4.0.4) and double checked for accuracy. When cross-over studies identified, only data from pre-cross-over period waere included. Additional information sought by contacting the corresponding authors when data were in a form unsuitable for meta-analysis. •Main outcome measures were ovulation, clinical pregnancy, miscarriage, multiple pregnancy, ovarian stimulation syndrome (OSS), total gonadotrophin dose used and total duration of stimulation. •Summary statistics were expressed as odds ratios with 95% CI calculated for each individual trial using Peto modification of Mantel-Haenszel method.	•Six RCTs were included: 3 RCTs (total of 457 women) compared rFSH with uFSH and 3 RCTs compared 2 different regimens of rFSH. •Pooled data from 3 RCTs comparing rFSH and uFSH showed no evidence of a difference between rFSH and uFSH in any of the outcomes. Pooling data from these studies was possible for clinical pregnancy per woman pregnancy rate (OR 0.95, 95% CI 0.64-1.41), multiple pregnancy rate (OR 0.44, 95% CI 0.16-1.21), miscarriage rate (OP 1.26, 95% CI 0.59-2.70) and OSS (OR 1.55, 95% CI 0.50-4.84). Data on ovarian date per cycle could be pooled from 2 studies (OR 1.19, 95% CI 0.78-1.80). Only 1 RCT reported data on ongoing pregnancy and none reported data on live birth. •There was no evidence of a difference between HMG and rFSH in clinical pregnancy, ongoing pregnancy, ovulation, miscarriage, OSS, and multiple pregnancy. •Data from 3RCTs comparing different dose regimens of rFSH could not be combined, and for each comparison there was insufficient evidence of a difference. There was insufficient evidence of a difference between chronic low dose step-up and conventional rFSH stimulation in terms of ovulation, clinical pregnancy, live birth, miscarriage, OSS, and multiple pregnancies. The OR for clinical pregnancy per woman was 1.62 (95% CI 0.64-4.07) for chronic low dose vs. conventional rFSH. The OR for clinical pregnancy per woman was 1.9 (95% CI 0.18-19.98) for a modified step-down vs. chronic low dose step-up protocol of rFSH. The OR for clinical pregnancy per woman was 0.79 (95% CI 0.12-4.96) for a starting dose of 37.5 IU vs. 50 IU in chronic low dose step-up protocols for rFSH stimulation (based on pre-cross-over data from one RCT). More RCTs with sufficient power are necessary to estimate the difference, if one exists, between rFSH and uFSH and between different dose regimens of rFSH.

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Table 5: Systematic reviews and meta-analyses (cont'd)

Study (authors, publication date, place)	Study's characteristics	Study's main findings and conclusions
Farquhar et al., [114] 2001 (update) Cochrane Menstrual Disorders and Subfertility Group, The Cochrane Collaboration Auckland, New Zealand	•This is an update of a systematic review conducted to determine the effectiveness and safety of laparoscopic ovarian drilling when compared with OI for sub-fertile women with CC-resistant PCOS. •The search strategy of the Menstrual Disorders and Subfertility Group was used for the identification of RCTs. A computerised MEDLINE search was used to identify non-RCTs (keywords of "polycystic ovary syndrome", "surgery, laparoscopic" and their various combinations and associated text words for titles and abstracts). •Trials were included if treatment consisted of laparoscopic ovarian drilling to induce ovulation in subfertile women with PCOS and compared with a concurrent control group. Of 15 trials identified, only 6 were included in the review (all RCTs). •All assessments of the quality of trials and data extraction were performed independently by 2 reviewers. Additional information on trial methodology and/or actual original trial data were sought from the authors of trials (which had unclear aspects of methodology or where the data was in a form unsuitable for meta-analysis). • The main outcomes were ovulation and pregnancy rates. Miscarriage rate, multiple pregnancy rate, and incidence of overstimulation and OHSS rate were secondary outcomes. •Rates between treatment arms were compared 6-12 mo after drilling with 3-6 cycles of gonadotrophins (which usually take 9-12 mo to administer). •The results for each study were combined for meta-analysis (using the Peto-modified Mantel-Haenszel method).	•Six RCTs were included: 4 compared ovarian drilling with gonadotrophins and 2 compared modalities of ovarian drilling. Overall, the methodological quality of these RCTs was poor. •The reviewed evidence showed that the ongoing pregnancy rate following ovarian drilling compared with gonadotrophins differed according to the length of follow up. Overall, the pooled OR (all studies) was NSS (OR 1.27, 95% CI 0.77, 1.98). •The 4 RCTs comparing ovarian drilling with gonadotrophins, did not demonstrate significant differences in ovarian and pregnancy rates between treatments at 6 and 12 months follow-up. Multiple pregnancy rates were reduced in the ovarian drilling arms of these RCTs (OR 0.16, 95%CI 0.03, 0.98). There was no difference in miscarriage rates in the drilling group when compared with gonadotrophin (OR 0.61, 955% 0.17, 2.16). •There is insufficient evidence of a difference in cumulative ongoing pregnancy rates between laparoscopic ovarian drilling after 6-12 months follow up and 3-6 cycles of ovulation induction with gonadotrophins as a primary treatment for subfertile women with anovulation (failure to ovulate) and PCOS. Multiple pregnancy rates are considerably reduced in those women who conceive following laparoscopic drilling. •In the absence of any direct comparison, laparoscopic drilling cannot be recommended in preference to clomiphene as a primary form of treatment for women with anovulatory PCOS. •In women who remain anovulatory after drilling the addition of clomiphene citrate or gonadotrophin therapy could be considered.

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Table 5: Systematic reviews and meta-analyses (cont'd)

Study (authors, publication date, place)	Study's characteristics	Study's main findings and conclusions*
Lord et al., [115] 2003 Cochrane Menstrual Disorders and Subfertility Group, The Cochrane Collaboration Devon, United Kingdom	•This is a systematic review conducted to assess the effectiveness of insulin sensitising drugs in improving clinical and biochemical features of PCOS. •The search strategy of the Menstrual Disorders and Subfertility Group was used to locate RCTs: - Electronic search of Coohrane Menstrual Disorders & Subfertility Group Trials Register (Dec 2002), Cochrane Central Register of Controlled Trials (Cochrane Library, Issue 4, 2002), MEDLINE (Jan 1966 to Dec 2002), and EMBASE (Jan 1985 to Dec 2002); used keywords: Polycystic Ovary Syndrome (PCOS); Metformin; Rosiglitazone; Pioglitazone; Troglitazone; D-chiro-Inositol; Insulin-lowering; Hypoglycemic agents; Biguanides; Plasminogen Activator Inhibitor-1; Hyperandrogenism; Hyperinsulinaemia. •Hand-search of reference sections of all trials obtained. All 12 pharmaceutical companies listed in the British National Formulary as manufacturing or distributing metformin, rosiglitazone, troglitazone and pioglitazone contacted in July 2001 for relevant data on all RCTs on their files, including unpublished trials. •Included RCTs investigating the effect of insulin sensitising drugs compared to placebo or no treatment, or compared to an OI agent. Data collection and analysis performed by 2 reviewers. Quality of selected RCT assessed independently by 2 reviewers; discrepancies solved by discussion. •Outcome measures defined as priority 1 (clinical) and priority 2 (biochemical) outcomes. Clinical outcomes included live birth rate; clinical pregnancy rate; spontaneous ovulation; menstrual cyclicity; body weight or BMI; waist circumference and waist-hip ratio; hirsutism; acne severity; BP; adverse pregnancy events (miscarriage and multiple pregnancy rates); and side effects. Biochemical outcomes included testosterone/other androgen levels; parameters measuring insulin sensitivity; fasting blood glucose level; stimulated glucose level; LDL and HDL cholesterol levels; triglyceride levels; and plasminogen activator inhibitor activity (PAI-1) levels. •The results were combined for meta-analysis (using the Peto-OR).	•Fifteen trials included for analysis (of these, 13 used metformin and included 543 participants). •Meta-analysis showed that metformin is effective in achieving ovulation in women with PCOS with OR of 3.88 (CI 2.25 to 6.69) for metformin versus placebo and OR of 4.41 (CI 2.37 to 8.22) for metformin and CC vs. CC alone. •An analysis of pregnancy rates suggests a significant treatment effect for metformin and CC compared to CC alone (OR 4.40, CI 1.96 to 9.85). However, few trials had pregnancy as a defined outcome measure, few controlled for other causes of infertility, and the possibility of publication bias limits confidence in this analysis. •Metformin has a significant effect in reducing fasting insulin levels (WMD -5.37, CI -8.11 to -2.63), blood pressure and low-density lipoprotein cholesterol (LDL). There was no evidence of effect on BMI or waist:hip ratio. •Metformin was associated with a significantly higher incidence of nausea, vomiting and other gastrointestinal disturbance, but no serious adverse effects were reported. •Metformin is an effective agent for anovulation in women with PCOS when used either alone or in combination with CC. Its choice as a first line agent seems justified, and there is some evidence of benefit on parameters of the metabolic syndrome. Ovulation rates are higher when combined with CC (76% versus 46% when used alone), but analysis is robust only in participants known to be previously resistant to CC. There is no evidence to indicate whether there is an increased multiple pregnancy rate with this combination. There is no data regarding its safety in long-term use in young women. It should be used as an adjuvant to general lifestyle improvements, and not as a replacement for increased exercise and improved diet.

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Table 5: Systematic reviews and meta-analyses (cont'd)

Study (authors, publication date, place)	Study's characteristics	Study's main findings and conclusions
Costello and Eden, [117] 2003 School of Women's and Children's Health, Division of Obstetrics and Gynaecology, University of New South Wales, Royal Hospital for Women, Sydney, New South Wales, Australia	*This is a systematic review conducted to review the effectiveness of metformin in restoring regular menstrual cycles and ovulation and achieving pregnancy in women with PCOS. *Reviewed studies were identified by electronic search of MEDLINE and EMBASE (1996 to June 2002). References of selected articles identified were hand-searched for additional relevant citations. Search terms: 'polycystic ovary syndrome', 'polycyctsic ovary disease', 'metformin', 'insulin sensitizing drugs', 'clomiphene ctrate', 'menstrual cycle', 'menstruation', 'menstruation inducing agent', 'ovulation', 'ovulation induction', and 'pregnancy'. *Inclusion criteria for selecting articles were based on study type (RCTs, controlled observational studies such as cohort and case-control studies, or uncontrolled observational descriptive studies not including case reports), patient selection (PCOS), intervention (exposure to metformin alone, metformin combined with other methods of ovulation iduction such as CC or gonadotrophin injections, or metformin combined with IVF). Selected articles included only those with original data. *The methodological standards of all studies were assessed according to *Guyat GH, Sackett DI, Cook DJ. Users' guides to the medical literature: II. How to use an article about therapy and prevention. A. Are the results of the study valid? JAMA 1993; 270:2598-601.*	*Thirty studies included: 12 RCTs, 2 cohort studies (one prospective and one retrospective), and 16 uncontrolled descriptive studies. *Due to a strong variability in metformin use according to study population, exposure, and outcome of interest, data from 12 RCTs was not combined for a meta-analysis. Eight of the 12 RCTs were small (including <50 patients randomized). Seven of the 12 RCTs included only CC resistant women. Two of the 12 RCTs involved use of metformin in the FSH OI and one in the IVF, and the reminder in the natural setting (metformin alone or combined with CC). *Data from controlled studies (almost all from RCTs) on mostly obese PCOS women demonstrate that metformin alone improves both restoration of regular menses and spontaneous ovulation, but there are no data supporting an improvement in pregnancy rate. The addition of metformin to CC results in an improved ovulation and pregnancy rate in both unselected and CC-resistant PCOS women. *The effectiveness and role of metformin in the treatment of PCOS anovulatory infertility in clinical practice is difficult to assess from currently available research. Further well-designed prospective, perhaps multicenter, RCTs with the primary end point of pregnancy or live-birth rate are required.

* - Main findings and conclusions regarding the outcomes of interest

REFERENCES

REFERENCES

1. *Dorland's Illustrated Medical Dictionary.* W. B. Saunders Company, editor. 9th Edition. Philadelphia, PA: W.B. Saunders Company; 1994.
2. Lenton EA. *Ovulation induction and ovarian stimulation.* In: Rodriguez-Armas O, Hedon B, Daya S, editors. Infertility and Contraception. Parthenon Publishing Group; 1998:p 128.
3. Macklon NS, Fauser BC. Progress in ovarian stimulation. *Ann Endocrinol (Paris)* 1999;60(2):137-42.
4. Solomon CG. The epidemiology of polycystic ovary syndrome. Prevalence and associated disease risks. *Endocrinol Metab Clin North Am* 1999;28(2):247-63.
5. Balen A. Ovulation induction for polycystic ovary syndrome. *Hum Fertil (Camb)* 2000;3(2):106-11.
6. Ben-Rafael Z, Orvieto R. *Infertility due to defective ovulation.* In: Rodriquez-Armas O, Hedon B, Daya S, editors. Infertility and Contraception. Parthenon Publishing Group; 1998:p 22-36.
7. *Overview of female infertility technologies.* Plymouth Meeting, PA: ECRI; 1993.
8. Marantides D. Management of polycystic ovary syndrome. *Nurse Pract* 1997;22(12):34-41.
9. ESHRE Capri Workshop. Guidelines of the diagnosis, treatment and management of infertility. *Hum Reprod* 1996;11:1775-807.
10. Nordenberg T. Overcoming infertility. Available: *http://www.pueblo.gsa.gov/cic_text/health/infertile/197_fert.html* (2001).
11. Kettel LM, Hummel WP. Ovulation induction in the estrogenized anovulatory patient. *Semin Reprod Endocrinol* 1996;14(4):309-15.
12. Hopkinson ZEC, Sattar N, Fleming R, Greer IA. Polycystic ovarian syndrome: the metabolic syndrome comes to gynaecology. *BMJ* 1998;317:329-32.
13. Adamson GD, Baker VL. Subfertility: causes, treatment and outcome. *Best Pract Res Clin Obstet Gynaecol* 2003;17(2):169-85.
14. Hamilton-Fairley D, Taylor A. Anovulation. *BMJ* 2003;327:546-8.
15. Collins JA, Hughes EG. Pharmacological interventions for the induction of ovulation. *Drugs* 1995;50(3):480-94.
16. Royal Commission Report. *Infertility treatments: fertility drugs.* Examination of Conditions, Technologies, and Practices; 1993.

17. Induction of ovulation. Available: *http://www.advancefertility.com/inducovu.htm* (2001).

18. Balen A. Anovulatory infertility and ovulation induction. Policy and Practice subcommittee of the British Fertility Society. *Hum Reprod* 1997;12(11 Suppl):83-7.

19. Larizgoitia I, Estrada M D, Garcia-Altes A. Recombinant-FSH as adjuvant in assisted reproduction: some data on the efficacy and efficiency of recombinant-FSH related to FSH of urinary origin. CAHTA; 2000. (BR02/2000): 16. Available: *http://www.aatm.es/cgi-bin/frame.pl/ang/pu.html.*

20. Daya S. *Definitions and factors affecting infertility.* In: Rodriguez-Armas O, Hedon B, Daya S, editors. Infertility and Contraception. Parthenon Publishing Group; 1998:p 4-7.

21. Vandermolen DT, Ratts VS, Evans WS, et al. Metformin increases the ovulatory rate and pregnancy rate from clomiphene citrate in patients with polycystic ovary syndrome who are resistant to clomiphene citrate alone. *Fertil Steril* 2001;75(2):310-5.

22. Hargreave TB, Mills JA. Investigating and management infertility in general practice. *BMJ* 1998;316:1438-41.

23. Leibowitz D, Hoffman J. Fertility drug therapies: past, present, and future. *JOGNN* 2000;29(2):201-10.

24. American Society of Reproductive Medicine (ASRM). Management of infertility caused by ovulatory dysfunction. *ACOG Practice Bulletin* 2002;99(2):347-58.

25. Pritts EA. Treatment of the infertile patient with polycystic ovarian syndrome. *Obstetrical & Gynecological Survey* 2002;57(9):587-97.

26. Kennedy HP, Griffin M, Frishman G. Enabling conception and pregnancy: midwifery care of women experiencing infertility. *J Nurse-Midwifery* 1998;43(3):190-207.

27. Crosignani PG, Bianchedi D, Riccaboni A, Vegetti W. Management of anovulatory infertility. *Hum Reprod* 1999;14(Suppl 1):108-19.

28. American Society of Reproductive Medicine (ASRM). Induction of ovarian follicle development and ovulation with exogenous gonadotropins. A practice committee report. A technical bulletin. ASRM 1998 Jun. Available: *http://www.asrm.com/Media/Practice/ovulation/html.*

29. Hughes E, Collins J, Vandekerckhove P. Clomiphene citrate for ovulation induction in women with oligo-amenorrhoea. In: *Cochrane Database Sys Rev* 2002;Issue 4, 2002.

30. The ESHRE Capri Workshop. Female infertility: treatment options for complicated cases. *Hum Reprod* 1997;12(6):1191-6.
31. Barnes RB. Diagnosis and therapy of hyperandrogenism. *Baillieres Clinical Obstetrics and Gynaecology* 1997;11(2):369-96.
32. Slowey MJ. Polycystic ovary syndrome: new perspective on an old problem. *South Med J* 2001;94(2):190-6.
33. Cahill DJ, Wardle PG. Management of infertility. *BMJ* 2002;325(7354):28-32.
34. Barbieri RL. Induction of ovulation in infertile women with hyperandrogenism and insulin resistance. *Am J Obstet Gynecol* 2000;183(6):1412-8.
35. Stein DE. Polycystic ovary syndrome. Available: *http://www.americaninfertility.org/pcos/aia_steinf.html* (2001 May 8).
36. Guzick D. Polycystic ovary syndrome: symptomatology, pathophysiology, and epidemiology. *Am J Obstet Gynecol* 1998;179(6 Pt 2):S89-S93.
37. Legro RS. Polycystic ovary syndrome: current and future treatment paradigms. *Am J Obstet Gynecol* 1998;179(6 Pt 2):S101-S108.
38. Homburg R. Adverse effects of luteinizing hormone on fertility: fact or fantasy. *Baillieres Clin Obstet Gynaecol* 1998;12(4):555-63.
39. Messinis IE, Milingos SD. Current and future status of ovulation induction in polycystic ovary syndrome. *Hum Reprod Update* 1997;3(3):235-53.
40. Kovacs G, Wood C. The current status of polycystic ovary syndrome. *Aust N Z J Obstet Gynaecol* 2001;41(1):65-8.
41. Buckett WM, Tan SL. Use of luteinizing hormone releasing hormone agonists in polycystic ovary syndrome. *Baillieres Clin Obstet Gynaecol* 1998;12(4):593-606.
42. Norman RJ, Kidson WJ, Cuneo RC, Zacharin MR, on behalf of the Endocrine Society of Australia tADSatAPEG. Metformin and intervention in polycystic ovary syndrome. Online Trader Position Statement2002 Nov 27. Available: *http://www.mja.com.au/public/issues/174_11_040601/norman/norman/html.*
43. American Society of Reproductive Medicine (ASRM). Use of insulin sensitizing agents in the treatment of polycystic ovary syndrome. *ASRM* 2000;A Practice Committee Report. A Committee Opinion.
44. Homburg R. Should patients with polycystic ovarian syndrome be treated with metformin? A note of cautious optimism. *Hum Reprod* 2002;17(4):853-6.
45. Legro RS. Polycystic ovary syndrome: the new millenium. *Molecular and Cellular Endocrinology* 2002;186(2):219-25.

46. Urman B, Sarac E, Dogan L, Gurgan T. Pregnancy in infertile PCOD patients. Complications and outcome. *J Reprod Med* 1997;42(8):501-5.

47. Royal College of Obstetricians and Gynaecologists. Long term consequences of polycystic ovary syndrome. *RCOG guideline* 2002;XX:1-8.

48. Homburg R, Howles CM. Low-dose FSH therapy for anovulatory infertility associated with polycystic ovary syndrome: rationale, results, reflections and refinements. *Hum Reprod Update* 1999;5(5):493-9.

49. Phipps WR. Polycystic ovary syndrome and ovulation induction. *Obstet Gynecol Clin North Am* 2001;28(1):165-82.

50. Wolf LJ. Ovulation induction. *Clin Obstet Gynecol* 2000;43(4):902-15.

51. Insulin-sensitising agents in polycystic-ovary syndrome (Commentary). *Lancet* 1998;351(9099):305-7.

52. Galtier-Dereure F, Pujol P, Dewailly D, Bringer J. Choice of stimulation in polycystic ovarian syndrome: the influence of obesity. *Hum Reprod* 1997;12(Suppl 1):88-96.

53. Balen A. Endocrine methods of ovulation induction. *Baillieres Clin Obstet Gynaecol* 1998;12(4):521-39.

54. Muriana A, Bucolo A, Scollo P. Prevention of premature LH surge during ovulation induction in polycystic ovarian syndrome: A randomized, comparative study between oral contraceptive/short term GnRH-analogue and depot GnRH-analogue protocols. *Ital J Gynaecol Obstet* 1999;11(2):52-6.

55. OG technical bulletin. Managing the anovulatory state: medical induction of ovulation. *Int J Gynaecol Obstet* 1994;47(3):305-12.

56. Royal College of Obstetricians and Gynaecologists. *The management of infertility in secondary care.* London,UK: RCOG Press; 1998:3.

57. Bennink HJTC, Fauser BCJM, Out HJ. Recombinant follicle-stimulating hormone (FSH; puregon) is more efficient than urinary FSH (Metrodin) in women with clomiphene citrate- resistant, normogonadotropic, chronic anovulation: A prospective, multicenter, assessor-blind, randomized, clinical trial. *Fertil Steril* 1998;69(1):19-25.

58. *Female infertility technologies. Part I: diagnosis and medical/surgical treatment.* Plymouth Meeting, PA : ECRI; 1994: no. 19.

59. Nugent D, Vandekerckhove P, Hughes E, et al. Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. In: *Cochrane Database Sys Rev* 2002;Issue 3, 2003.

60. Jacobs HS, Agrawal R. Complications of ovarian stimulation. *Baillieres Clin Obstet Gynaecol* 1998;12(4):565-79.

61. HKCOG Guidelines. *Guidelines for use of gonadotrophins.* The Hong Kong College of Obstetricians and Gynaecologists, editor. Hong Kong: 1997:1.

62. Yong EL, Ng SC, Chan C, et al. Responses of polycystic ovarian syndrome and related variants to low-dose follicle stimulating hormone. *Int J Gynaecol Obstet* 1997;57(3):305-11.

63. Hughes E, Collins J, Vandekerckhove P. Clomiphene citrate for unexplained subfertility in women. In: *Cochrane Database Sys Rev* 2002;Issue 4, 2002.

64. Boostanfar R, Jain JK, Mishell DR, Jr., Paulson RJ. A prospective randomized trial comparing clomiphene citrate with tamoxifen citrate for ovulation induction. *Fertil Steril* 2001;75(5):1024-6.

65. Out HJ. Should treatment with clomiphene continue? Available: *http://www.kenes.com/controbersies/prog.htm* (2002 Aug 16).

66. Imani B, Eijkemans MJC, van ter Velde EG, et al. Predictors o f chances to conceive in ovulatory patients during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheïc infertility. *J Clin Endocrinol Metab* 1999;84(5):1617-22.

67. Fridstrom M, Sjoblom P, Granberg M, Hillensjo T. A cost comparison of infertility treatment for clomiphene resistant polycystic ovary syndrome. *Acta Obstet Gynecol Scand* 1999;78(3):212-6.

68. Vegetti W, Testa G, Ragni G, et al. Ovarian stimulation with low-dose pure follicle-stimulating hormone in polycystic ovarian syndrome anovulatory patients: effect of long-term pretreatment with gonadotrophin-releasing hormone analogue. *Gynecol Obstet Invest* 1998;45(3):186-9.

69. Hunter MI, DeCherney AH. Ovulation induction in non-ART cycles. *Reproductive Technologies* 2000;10(2):82-5.

70. Daya S. Cost-effective, evidence-based infertility care. *Curr Opin in Obstet Gynecol* 2000;12(3):227-31.

71. Imani B, Eijkemans MJ, te Velde ER, et al. Predictors of patients remaining anovulatory during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. *J Clin Endocrinol Metab* 1998;83(7):2361-5.

72. Kocak M, Caliskan E, Simsir C, Haberal A. Metformin therapy improves ovulatory rates, cervical scores, and pregnancy rates in clomiphene citrate-resistant women with polycystic ovary syndrome. *Fertil Steril* 2002;77(1):101-6.

73. InterNational Council on Infertility Information Dissemination. Clomid use and abuse. Clomiphene citrate (clomid, serophene). Available: *http://www.inciid.org/clomidberger.html* (accessed 2001 May 17).

74. Bissonnette F, Lapensee L. Investigating and treating infertility: how far have we come? Part 1. *Cdn J Diag* 2001;January:65-73.

75. Lidor AL, Goldenberg M, Cohen SB, et al. Management of women with polycystic ovary syndrome who experienced premature luteinization during clomiphene citrate treatment. *Fertil Steril* 2000;74(4):749-52.

76. Suginami H, Kitagawa H, Nakahashi N, Yano K, Matsubara K. A clomiphene citrate and tamoxifen citrate combination therapy: a novel therapy for ovulation induction. *Fertil Steril* 1993;59(5):976-9.

77. International Recombinant Human Chorionic Gonadotropin Study Group. Induction of ovulation in World Health Organization group II anovulatory women undergoing follicular stimulation with recombinant human follicle-stimulating hormone: a comparison of recombinant human chorionic gonadotropin (rhCG) and urinary hCG. *Fertil Steril* 2001;75(6):1111-8.

78. Yarali H, Bukulmez O, Gurgan T. Urinary follicle-stimulating hormone (FSH) versus recombinant FSH in clomiphene citrate-resistant, normogonadotropic, chronic anovulation: a prospective randomized study. *Fertil Steril* 1999;72(2):276-81.

79. Homburg R. Effects of different gonadotrophin preparations in the management of anovulation. Available: *http://www.obgyn.net/firstcontrobersies/prague1999index.htm* (1999 Aug 16).

80. Bayram N, van Wely M, van d, V. Recombinant FSH versus urinary gonadotrophins or recombinant FSH for ovulation induction in subfertility associated with polycystic ovary syndrome. In: *Cochrane Database Sys Rev* 2002;Issue 3, 2003.

81. Egbase PE. Severe OHSS: how many cases are preventable? *Hum Reprod* 2000;15(1):8-10.

82. Bider D, Blankstein J, Levron J, Tur-Kaspa I. Gonadotropins and glucocorticoid therapy for "low responders"--a controlled study. *J Assist Reprod Genet* 1997;14(6):328-31.

83. Balasch J, Fabregues F, Creus M, et al. Follicular development and hormone concentrations following recombinant FSH administration for anovulation associated with polycystic ovarian syndrome: prospective, randomized comparison between low-dose step-up and modified step-down regimens. *Hum Reprod* 2001;16(4):652-6.

84. Ron-El R, Raziel A, Schachter M, et al. Induction of ovulation after GnRH antagonists. *Hum Reprod Update* 2000;6(4):318-21.

85. Filicori M. The role of luteinizing hormone in folliculogenesis and ovulation induction. *Fertil Steril* 1999;71(3):405-14.

86. Ergur AR, Yergok YZ, Ertekin A, et al. Clomiphene citrate-resistant polycystic ovary syndrome. Preventing multifollicular development. *J Reprod Med* 1998;43(3):185-90.

87. Hughes E, Collins J, Vandekerckhove P. Gonadotrophin-releasing hormone analogue as an adjunct to gonadotropin therapy for clomiphene-resistant polycystic ovarian syndrome. In: *Cochrane Database Syst Rev* 2000;(2).

88. Homburg R, Levy T, Ben Rafael Z. Adjuvant growth hormone for induction of ovulation with gonadotrophin-releasing hormone agonist and gonadotrophins in polycystic ovary syndrome: a randomized, double-blind, placebo controlled trial. *Hum Reprod* 1995;10(10):2550-3.

89. Homburg R. Growth hormone and fertility--clinical studies. *Horm Res* 1996;45(1-2):81-5.

90. Sturrock ND, Lannon B, Fay TN. Metformin does not enhance ovulation induction in clomiphene resistant polycystic ovary syndrome in clinical practice. *Br J Clin Pharmacol* 2002;53(5):469-73.

91. Barbieri RL. Metformin for the treatment of polycystic ovary syndrome. *Obstet Gynecol* 2003;101(4):785-93.

92. Haas DA, Carr BR, Attia GR. Effects of metformin on body mass index, menstrual cyclicity, and ovulation induction in women with polycystic ovary syndrome. *Fertil Steril* 2003;79(3):469-81.

93. Harborne L, Fleming R, Lyall H, et al. Descriptive review of the evidence for the use of metformin in polycystic ovary syndrome. *Lancet* 2003;361:1894-901.

94. Ghazeeri G, Kutteh WH, Bryer-Ash M, et al. Effect of rosiglitazone on spontaneous and clomiphene citrate-induced ovulation in women with polycystic ovary syndrome. *Fertil Steril* 2003;79(3):562-6.

95. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. *Ovarian stimulation in infertility.* Report: 2000.

96. Lupron/Zoladex. Coverage Policy Bulletins Number 05012001 Apr 27. Available: *http://www.aetna.com/cpb/data/CPBA0501.html.*

97. Infertility Coverage. Coverage Policy Bulletins Number: 03272002 Nov 15. Available: *http://www.aetna.com/cpb/data/CPBA0327.html.*

98. Injectable Medication Coverage. Coverage Policy Bulletins Number 00202002 Dec 11. Available: *http://www.aetna.com/cpb/data/CPBA0020.html.*

99. Arkansas Foundation for Medical Care. Medicaid drug cost comparisons. Available: *http://www.americaninfertility.org/pcos/aia_steinf.html* (accessed 2004 Jan 14).

100. Collins JA, Feeny D, Gunby J. The cost of infertility diagnosis and treatment in Canada in 1995. *Hum Reprod* 1997;12(5):951-8.

101. Jarrell JF, Seidel J, Bigelow P. *Adverse effects of drugs used for ovulation induction.* In: Royal Commission on New Reproductive Technologies, editor. New Reproductive Technologies and the Health Care System: The Case for Evidence-Based Medicine; Volume 11. Ottawa, ON: Royal Commission on New Reproductive Technologies; 1991:p 453-530.

102. Allan BB, Brant R, Seidel JE, Jarrell JF. Declining sex ratios in Canada. *CMAJ* 1997;156(1):37-41.

103. Jarrell J. Rationale for the study of the human sex ratio in population studies of polluted environments. *Cad Saude Publica* 2002;18(2):429-34.

104. Health Canada. Drug Product Database (DPD). Available: *http://www.hc-sc.gc.ca/drug2/product/p19347.html* (2002 Dec 2).

105. SOGC Committee Opinion. *Economics of fertility treatment.* Ottawa, ON: SOGC; 1994:11.

106. Serono-Canada. Insurance information. Available: *http://www.serono-canada.com/english/solution/reproduct/insuranc/htm* (2001 May 17).

107. Timmerman-van Kessel ECM, Cikot RJLM, Dargel-Donkers EJH, et al. A randomized controlled study comparing the endocrine effects of pulsatile intravenous gonadotropin-releasing hormone after gonadotropin-releasing hormone agonist pretreatment versus clomiphene citrate in patients with polycystic ovary syndrome. *Fertil Steril* 2000;73(6):1145-8.

108. Hassan HA, El Gezeiry D, Nafaa TM, Baghdady I. Improved responsiveness of PCOS patients to clomiphene after CYP17a inhibitor. *J Assisted Reprod Genetics* 2001;18(11):608-11.

109. Parsanezhad ME, Alborzi S, Jahromi BN. A prospective, double-blind, randomized, placebo-controlled clinical trial of bromocriptine in clomiphene-resistant patients with polycystic ovary syndrome and normal prolactin level. *Int J Fertil Womens Med* 2002;47(6):272-7.

110. Hugues JN, Cedrin-Durnerin I, Avril C, et al. Sequential step-up and step-down dose regimen: an alternative method for ovulation induction with follicle-stimulating hormone in polycystic ovarian syndrome. *Hum Reprod* 1996;11(12):2581-4.

111. George SS, George K, Irwin C, et al. Sequential treatment of metformin and clomiphene citrate in clomiphene-resistant women with polycystic ovary syndrome: a randomized, controlled trial. *Hum Reprod* 2003;18(2):299-304.

112. Ramzy A-M, El Kateb S, Al Inany H, et al. The use of metformin in overweight and lean infertile patients with polycystic ovarian syndrome: A randomized controlled trial. *Middle East Fertil Soc J* 2003;8(2):143-9.

113. Bayram N, van Wely M, Vandekerckhove P, et al. Pulsatile luteinising hormone releasing hormone for ovulation induction in subfertility associated with polycystic ovary syndrome. In:*Cochrane Database Sys Rev* 2002;Issue 3, 2003.

114. Farquhar C, Vandekerckhove P, Arnot M, Lilford R. Laparoscopic "drilling" by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome. In: *Cochrane Database Sys Rev* 2002;Issue 3, 2003.

115. Lord J, Flight I, Norman R. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. In: *Cochrane Database Syst Rev* 2003;3.

116. van Wely M, Bayram N, van d, V. Recombinant FSH in alternative doses or versus urinary gonadotrophins for ovulation induction in subfertility associated with polycystic ovary syndrome: a systematic review based on a Cochrane review. *Hum Reprod* 2003;18(6):1143-9.

117. Costello MF, Eden JA. A systematic review of the reproductive system effects of metformin in patients with polycystic ovary syndrome. *Fertil Steril* 2003;79(1):1-13.

118. FDA. ACTOS (pioglitazone HCI): AVANDIA (rosiglitazone maleate). Available: *http://www fda gov/medwatch/SAFETY/2002/summary-actos-avandia pdf* (accessed 2004 Jan 8).

119. Corchia C, Mastroiacovo P, Lanni R, et al. What proportion of multiple births are due to ovulation induction? A register-based study in Italy. *Am J Public Health* 1996;86(6):851-4.

120. Gleicher N, Oleske DM, Tur-Kaspa I, et al. Reducing the risk of high-order multiple pregnancy after ovarian stimulation with gonadotropins. *N Engl J Med* 2000;343(1):2-7.

121. Bhattacharya S, Templeton A. In treating infertility, are multiple pregnancies unavoidable? *N Engl J Med* 2000;343(1):56-9.

122. Elchalal U, Schenker JG. The pathophysiology of ovarian hyperstimulation syndrome -- views and ideas. *Hum Reprod* 1997;12(6):1129-37.

123. Hammond KR. The role of ovulation induction and ultrasonography: a practical assessment. *Infert Reprod Med Clin N Am* 1996;7(3):427-41.

124. Meirow D, Schenker JG. The link between female infertility and cancer: epidemiology and possible aetiologies. *Hum Reprod Update* 1996;2(1):63-75.

125. Royal College of Obstetricians and Gynaecologists. *The management of infertility in tertiary care.* London, UK: RCOG Press; 2000: No. 6.

126. Hughes E, Collins J, Vandekerckhove P. Ovulation induction with urinary follicle stimulating hormone versus human menopausal gonadotropin for clomiphene-resistant polycystic ovary syndrome. In: *Cochrane Database Sys Rev* 2002;Issue 4, 2002.

127. Bayram N, van Wely M, van der Veldt V. Recombinant FSH versus urinary gonadotrophins or recombinant FSH for ovulation induction in subfertility associated with polycystic ovary syndrome. In: *Cochrane Database Syst Rev* 2003;(3).

128. Lord JM, Flight IHK, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ* 2003;327:1-6.

129. Hedon B, Hugues JN, Emperaire JC, et al. A comparative prospective study of a chronic low dose versus a conventional ovulation stimulation regimen using recombinant human follicle stimulating hormone in anovulatory infertile women. *Hum Reprod* 1998;13(1O):2688-92.

130. Mendes MC, Ferriani RA, Sala MM, et al. Induction of ovulation with clomiphene citrate in combination with metoclopramide in patients with amenorrhea of hypothalamic origin. *Gynecol Endocrinol* 1999;13(3):149-54.

131. Bayram N, von Wely M, Bossuyt P, von Veen F. Randomized clinical trial of laparoscopic electrocoagulation of the ovaries versus recombinant FSH for ovulation induction in subfertility associated with polycystic ovary syndrome. *Fertil Steril* 2001;76(3):O113.

132. Ernest NH, Flora TO, William SW, Ho PC. A prospective, open, randomized clinical study to assess the efficacy and safety of two gonadotropin preparations administered in WHO Group II anovulatory subfertile women. *J Obstet Gynaecol Res* 1998;24(5):355-61.

133. Shalev E, Geslevich Y, Matilsky M, Ben Ami M. Gonadotrophin-releasing hormone agonist compared with human chorionic gonadotrophin for ovulation induction after clomiphene citrate treatment. *Hum Reprod* 1995;10(10):2541-4.

134. Bider D, Menashe Y, Goldenberg M, Dulitzky M, Lifshitz A, Dor J. Dexamethasone as an adjuvant therapy for anovulatory, normoandrogenic patients during ovulation induction with exogenous gonadotropins. *J Assist Reprod Genet* 1996;13(8):613-6.

135. Nichols J, Knochenhauer E, Fein SH, et al. Subcutaneously administered Repronex in oligoovulatory female patients undergoing ovulation induction is as effective and well tolerated as intramuscular human menopausal gonadotropin treatment. *Fertil Steril* 2001;76(1):58-66.

136. De Vita V. Bromocriptine + gonadotropin vs goserelin + gonadotropin in the induction of ovulation in patients with ovarian polycystosis. *Minerva Ginecol* 1995;47(3):93-7.

137. Lass A, Vassiliev A, Decosterd G, et al. Relationship of baseline ovarian volume to ovarian response in World Health Organization II anovulatory patients who underwent ovulation induction with gonadotropins. *Fertil Steril* 2002;78(2):265-9.

138. van Weissenbruch MM, Schoemaker HC, Drexhage HA, Schoemaker J. Pharmaco-dynamics of human menopausal gonadotrophin (HMG) and follicle-stimulating hormone (FSH). The importance of the FSH concentration in initiating follicular growth in polycystic ovary-like disease. *Hum Reprod* 1993;8(6):813-21.

139. van Santbrink EJ, Fauser BC. Urinary follicle-stimulating hormone for normogonadotropic clomiphene-resistant anovulatory infertility: prospective, randomized comparison between low dose step-up and step-down dose regimens. *J Clin Endocrinol Metab* 1997;82(11):3597-602.

140. Nestler JE, Jakobowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *N Engl J Med* 1998;338(26):1876-80.

141. De Leo V, La Marca A, Ditto A, et al. Effects of metformin on gonadotropin-induced ovulation in women with polycystic ovary syndrome. *Fertil Steril* 1999;72(2):282-5.

142. Farquhar CM, Williamson K, Gudex G, et al. A randomized controlled trial of laparoscopic ovarian diathermy versus gonadotropin therapy for women with clomiphene citrate-resistant polycystic ovary syndrome. *Fertil Steril* 2002;78(2):404-11.

143. Yarah H, Yildiz BO, Deminol A, et al. Co-administration of metformin during rFSH treatment in patients with clomiphene citrate-resistant polycystic ovarian syndrome: a prospective randomized trial. *Hum Reprod* 2002;17(2):289-94.

144. Pearce JM, Hamid RI. Randomised controlled trial of the use of human chorionic gonadotrophin in recurrent miscarriage associated with polycystic ovaries. *Br J Obstet Gynaecol* 1994;101(8):685-8.

145. Andoh K, Mizunuma H, Liu X, et al. A comparative study of fixed-dose, step-down, and low-dose step-up regimens of human menopausal gonadotropin for patients with polycystic ovary syndrome. *Fertil Steril* 1998;70(5):840-6.

146. Prelevic GM, Ginsburg J, Maletic D, et al. The effects of the somatostatin analogue octreotide on ovulatory performance in women with polycystic ovaries. *Hum Reprod* 1995;10(1):28-32.

147. Branigan EF, Estes MA. A randomized clinical trial of treatment of clomiphene citrate-resistant anovulation with the use of oral contraceptive pill suppression and repeat clomiphene citrate treatment. *Am J Obstet Gynecol* 2003;188(6):1424-30.

148. Wang HS, Soong YK. Transvaginal progesterone supplementation increases serum insulin-like growth factor-binding protein-1 levels. *Gynecol Endocrinol* 1996;10(5):349-55.

149. Homburg R, Levy T, Ben Rafael Z. A comparative prospective study of conventional regimen with chronic low-dose administration of follicle-stimulating hormone for anovulation associated with polycystic ovary syndrome. *Fertil Steril* 1995;63(4):729-33.

150. Kotarba D, Kotarba J, Hughes E. Growth hormone for in vitro fertilization. In: *Cochrane Database Sys Rev* 2002;Issue 4, 2002.

151. RxList Monographs. Clomiphene. Available: *http://www.rxlist.com/cgi/generic/clomiph_wcp.htm* (2001).

152. Treatment of anovulation. Available: *http://www.medlib.med.utah.edu/kw/human_reprod/seminars/seminar2E.html* (2001).

153. Goshen R, Weissman A, Shoham Z. Epithelial ovarian cancer, infertility and induction of ovulation: possible pathogenesis and updated concepts. *Baillieres Clin Obstet Gynaecol 1998*;12(4):581-91.

154. Bristow RE, Karlan BY. Ovulation induction, infertility, and ovarian cancer risk. *Fertil Steril* 1996;66(4):499-507.

155. Nieto JJ, Rolfe KJ, MacLean AB, Hardiman P. Ovarian cancer and infertility: a genetic link? *Lancet* 1999;354:649.

156. FDA. Avandia (rosiglitazone nialeate) tablets. Available: *http://www pharmcast com/WarningLetters/Oct2000/SKB1000 htm* (accessed 2004 Jan 8).